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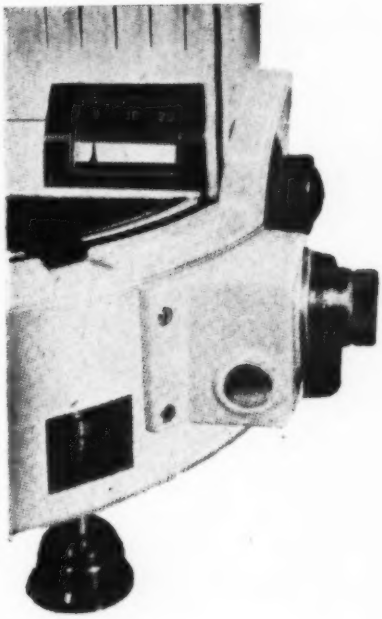

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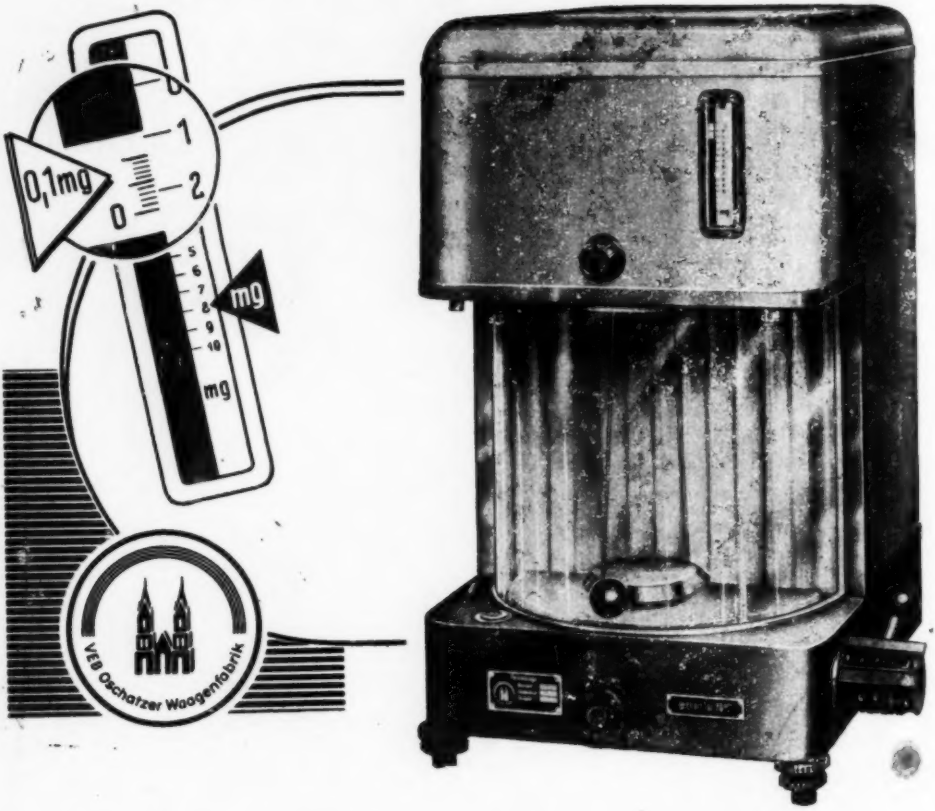

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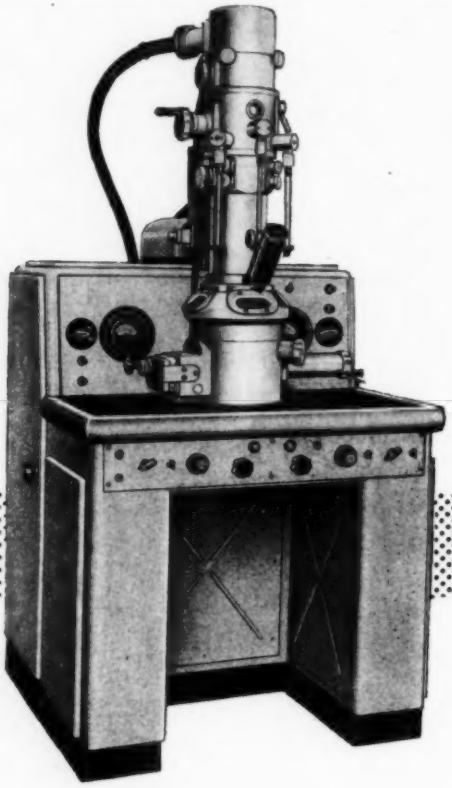

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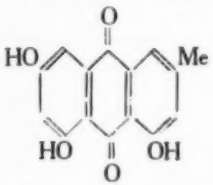
[Jour. Indian Chem. Soc., Vol. 37, No. 5, 1960]

NEW METHODS FOR THE SYNTHESIS OF NATURALLY OCCURRING ANTHRAQUINONES*

K. VENKATARAMAN

Naturally occurring anthraquinone derivatives with one or two possible exceptions are no longer of interest as colouring matters, but their physiological properties appear to justify further study. Hydroxyanthraquinones containing *C*-methyl, hydroxymethyl, carboxyl and glycosidic groups have long been known to be present in cathartic drugs such as rhubarb, senna, cascara and aloes, from some of which anthrones and anthranols have also been isolated. Stoll[1] showed that the active cathartic constituents of senna, sennoside A and B, are derivatives of 10, 10′-dianthronyl. 2-Methylanthraquinone, purpurin, emodin (I), aloe-emodin (II), rhein (III) and barbaloin have been reported to have antibacterial and antitubercular properties.[2]



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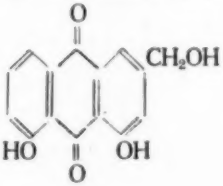

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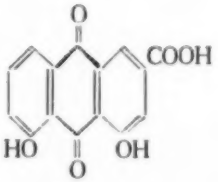


(III)

Three different lines of investigation led to the suggestion that *iso*nicotinic acid hydrazide killed tubercle bacilli through the intracellular accumulation of hydrogen peroxide;[3] but subsequent work[4] showed that the hypothesis was untenable. Holman[5] observed that hydrogen peroxide had a curative action on tumours in rats and humans; other workers, [6, 7, 8, 9] have failed to confirm this, but Sugiura found that a dose of 225 mg./kg. of hydrogen peroxide had a moderate inhibitory effect on sarcoma 180 ascites tumour in rats.[9] Although from the available evidence it is very improbable that hydrogen peroxide plays any part in antitubercular or antitumour activity, the physiological properties of anthraquinone derivatives are of additional interest because of the observation made by Manchot and Herzog in 1901[10] that hydrogen peroxide is formed when anthrahydroquinone (9,10-dihydroxyanthracene) absorbs oxygen; incidentally, the reduction-oxidation of 2-ethylanthraquinone or 2- *t*-butylanthraquinone is now used for the manufacture of hydrogen peroxide.

At an early stage of our attempts to synthesise a series of naturally occurring anthraquinones and their analogues for an examination of their antitubercular and other physiological properties, it became obvious that the known methods, [11] which were usually based on the condensation of nitro- or methoxyphthalic anhydrides with phenols or their ethers, were dependent on relatively inaccessible intermediates and also unsatisfactory from other points of view. Routes starting from common anthraquinonoid dye intermediates were therefore sought, partly because of a wider interest in the reactions of anthraquinone and anthrone derivatives in relation to constitutional problems concerning vat dyes.[10,12]

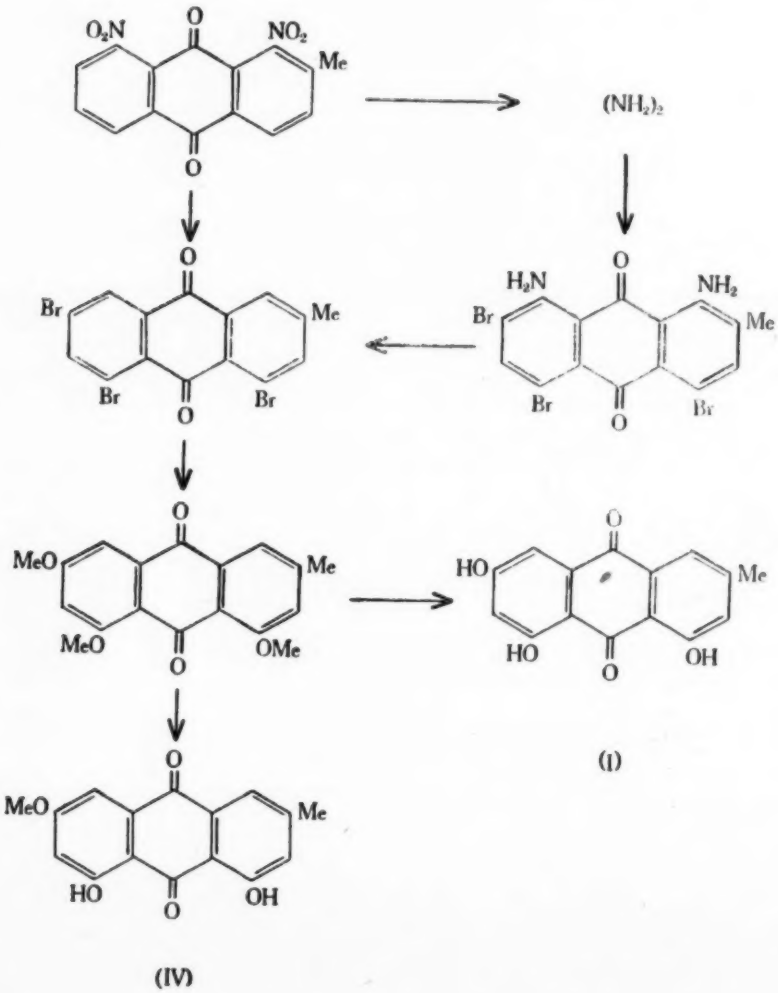
Charts I and II illustrate the preparation of emodin (I), physcion (IV), chrysophanol (V), islandicin (VI) and rhein (III) from 1, 5-dinitro-and 1, 8-dinitro-2-methylanthraquinone.[13] After

*Presidential address delivered at the 36th Annual General Meeting of the Indian Chemical Society, held in Bombay on Monday, January 4, 1960.

the dinitration of 2-methylanthraquinone and separation of the isomers (A. Locher and H. E. Fierz, 1927), a series of reactions are involved, but in general they proceed without difficulty and in good yield.[2] Experimental conditions for some of the stages have been recently improved; they will be described elsewhere, but a few points may be mentioned. The replacement of chlorine or bromine in α- or β-positions (the latter naturally requiring more vigorous treatment) by methoxyl can be effected in over 80% yield; refluxing with sodium methoxide and copper oxide in methanol for 48-72 hours usually gives better yields than heating in a sealed tube at 160-70° for 6-12 hours. Complete demethylation of emodin trimethyl ether to emodin (I) is best effected by heating for a few minutes with aluminium chloride-sodium chloride at 140-50°, and partial demethylation to

CHART I

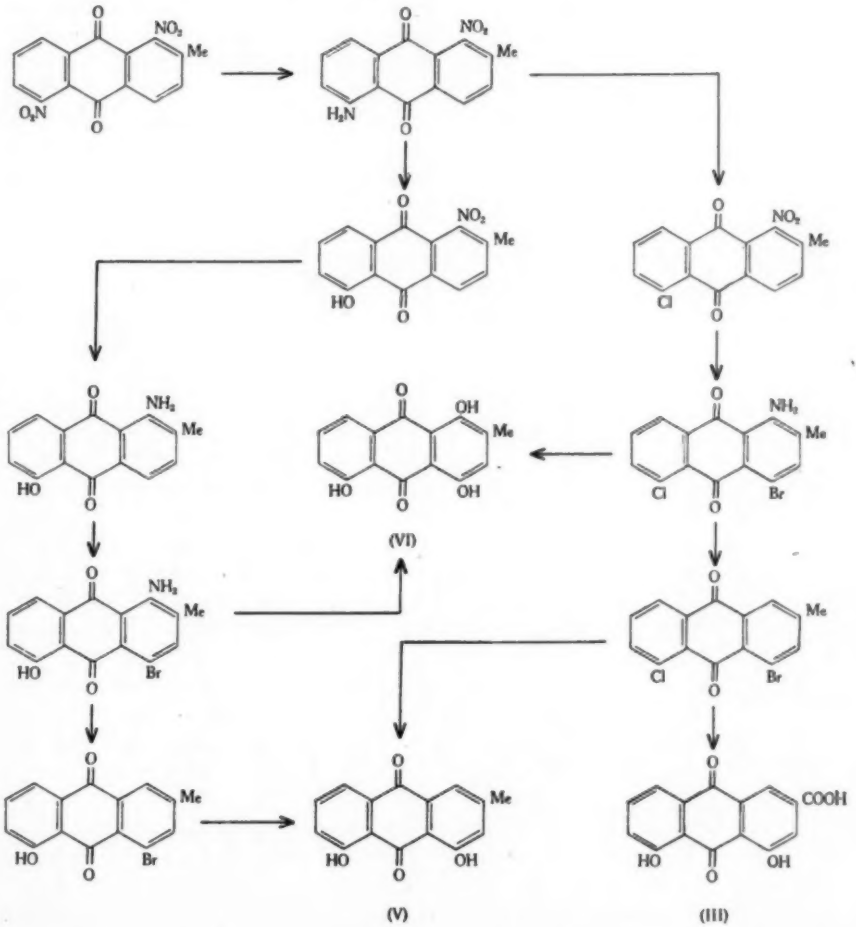
Emodin and Physcion from 1, 8-Dinitro-2-methylanthraquinone.



physcion (IV) by refluxing with hydrobromic acid in acetic acid for an hour. When 1-amino-5-hydroxy-2-methylanthraquinone (Chart II) is treated with bromine in glacial acetic acid at 20°, the hydroxylated ring is unaffected and the sole product is the 4-bromo compound. The replacement of chlorine or bromine in the α-position by hydroxyl takes place on heating with lime and copper bronze or copper oxide in a sealed tube at 200-10° for 24 hours, but for replacing a β-halogen the temperature has to be raised to 230-50°.

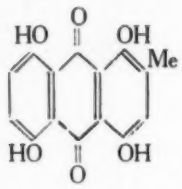
CHART II

Chrysophanol, Islandicin and Rhein from 1, 5-*Dinitro-2-methylanthraquinone.*



Islandicin (VI) and cynodontin (VII) have been recently synthesised by the persulphate oxidation of the benzoylbenzoic acids (VIII; R = H or OMe), followed by cyclization and

demethylation.[14] As in some of the older methods, this involves the preparation of a mono- or dimethoxyphthalic anhydride.



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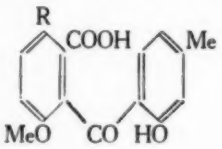
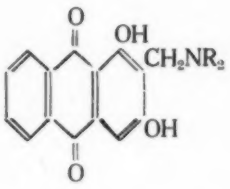


(VIII)

The Marschalk reaction for C-alkylation of amino- and hydroxyanthraquinones by the action of aldehydes in the presence of alkaline hydrosulphite is useful for the synthesis of 2-methylanthraquinone derivatives such as rubiadin (1, 3-dihydroxy-2-methylanthraquinone), which Jones and Robertson prepared earlier by two tedious methods involving 2, 6-dichlorotoluene or 2-methoxy-6-nitrotoluene.[2] Marschalk prepared 1-amino-5-chloro-2-methylanthraquinone from 1-amino-5-chloroanthraquinone, an intermediate for Indanthrene Golden Orange 3G; but in this case the method shown in Chart II is more satisfactory. Other applications of the Marschalk reaction are the synthesis of soranjidiol (1, 6-dihydroxy-2-methylanthraquinone) from 1-hydroxy-6-methoxyanthraquinone, which is C-methylated in the 2-position and then demethylated, and the synthesis of morindone (1, 5, 6-trihydroxy-2-methylanthraquinone) from 1, 2, 5-trihydroxyanthraquinone (Brilliant Alizarin Bordeaux R) by direct C-methylation in the 6-position or through the 2-methyl ether. Alizarin does not undergo the Marschalk reaction under the usual conditions. Morindone brominates in the 7-position, and the further action of lime under pressure should lead to copareolatin (1, 5, 6, 7-tetrahydroxy-2-methylanthraquinone), isolated by Briggs[2] from *Coprosma areolata*, a New Zealand plant.[15]

Xanthopurpurin and purpurin readily undergo a Mannich base reaction with formaldehyde and dialkylamines at room temperature, yielding (IX) and (X).[16] Such basic derivatives of anthraquinone may have interest from several points of view because of their physical and chemical properties. Dimethylaminomethylxanthopurpurin (IX: R = Me) was kindly tested by Dr. V. C. Barry, who reported in January 1958 that it partially inhibited *M. tuberculosis* (H37Rv; Proskauer and Beck medium containing 5% human serum) at a dilution of 100,000; the anthraquinone ring in this case has probably little significance, since a similar Mannich base from orcinol-γ-carboxylic acid exhibited activity of the same order. Purpurin condenses smoothly with formaldehyde and diethanolamine to form (X; R = CH_2CH_2OH), from which (XI) can be prepared; (XI) may be of some interest in cancer studies as a biological alkylating agent and as a quinone with metal-chelating properties. The only reference in the literature to a Mannich base condensation in the anthraquinone series, other than the cited patent,[16] is the preparation of the Mannich bases from formaldehyde, iminodiacetic acid and alizarin, 1,2,5-, 1,2,6- and 1,2,7-trihydroxyanthraquinones, and quinalizarin;[17] "very little nitrogenous product was obtained from the corresponding reaction with 2-hydroxy-, 1, 4-, 1,5-, or 1, 8-dihydroxy-, or 1, 2, 3- or 1, 2, 4-trihydroxyanthraquinone." The reaction was carried out at 75°, using excess of the aldehyde and acid (as the disodium salt), and the products (obtained as yellow or orange-brown powders in 13% yield from alizarin and unspecified yield in the other cases) were examined as complexometric indicators in EDTA titrations.[17] It is doubtful if the products described by Belcher, Leonard and West[17] had the structures ascribed to them. On the other hand purpurin, which they found to be

unreactive, reacts readily with formaldehyde and iminodiacetic acid at room temperature, yielding (X; R = CH_2COOH) as red needles.[16]



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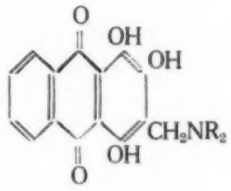

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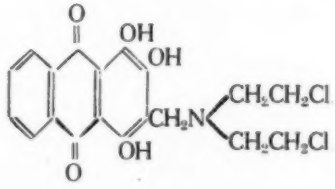
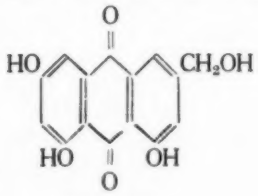


(XI)

Derivatives of 2-Anthraquinonylcarbinol and Anthraquinone-2-aldehyde

Mitter and Banerjee in 1932 converted rhein diacetate into aloe-emodin (II) in unspecified yield via the acid chloride and aldehyde, and until a few years ago this was the only synthesis of a natural anthraquinonylcarbinol. Brown and Subba Rao have described the reduction of carboxylic acids to the corresponding primary alcohols by sodium borohydride-aluminium chloride in diglyme or by diborane in any ether medium.[18] Preliminary experiments showed that the former procedure was not suitable for the reduction of anthraquinone carboxylic acids containing hydroxyl or acetoxyl groups; but rhein diacetate in diglyme (diethylene glycol dimethyl ether) or monoglyme (ethylene glycol dimethyl ether) underwent smooth reduction to the carbinol by passing diborane (generated by adding a diglyme solution of sodium borohydride to boron trifluoride-etherate in diglyme) at room temperature until an intense orange to red colour developed. Hydrolysis of the product with cold dilute sodium hydroxide solution gave aloe-emodin (II) in an overall yield of about 60%. Citreorosein (XII; ω-hydroxyemodin), a metabolite of *Penicillium citreo-roseum* and *P. cyclopium*,[11] was similarly prepared from emodic acid triacetate (XIII).[19] Natural citreorosein for comparison was kindly supplied by Professor T. Posternak.



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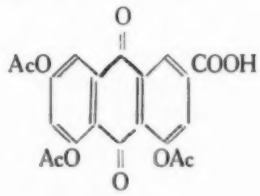
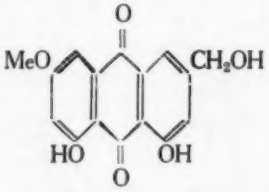


(XIII)

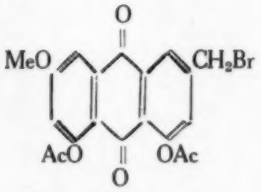
An important feature of the action of diborane on anthraquinone-2-carboxylic acids was the preferential reduction of the carboxyl group, the quinone group being attacked only at a later stage. In this connection it seemed desirable to examine the action of a mixture of sodium borohydride

and boron trifluoride-etherate, as distinct from diborane, on anthraquinone derivatives, and a new general method for their reduction to anthracene derivatives thus became available. When a suspension of anthraquinone in diglyme was treated successively with sodium borohydride and boron trifluoride-etherate, both in diglyme, at 25-30° with agitation for two hours, anthracene was obtained in about 70% yield.[20] By varying the conditions slightly the following reductions could be carried out: 1-chloroanthraquinone → 1-chloroanthracene ; 2-chloroanthraquione → 2-chloroanthracene ; 2-aminoanthraquinone → 2-aminoanthracene ; 2-hydroxyanthraquinone → 2-hydroxyanthracene ; 2-methoxyanthraquinone → 2-methoxyanthracene ; anthraquinone-2-carboxylic acid → anthracene-2-carbinol ; 3, 4, 9, 10-dibenzopyrene-5, 8-quinone → 3, 4, 9, 10-dibenzopyrene;[21] 2-methyl-1,4-naphthoquinone → 2-methylnaphthalene. This new procedure for the reduction of anthraquinones to anthracene derivatives promises to be useful for investigating the constitution of naturally occurring quinones as well as anthraquinonoid vat dyes.

Teloschistin, isolated by Seshadri[22] from the Indian lichen *Teloschistes flavicans*, and fallacinol, isolated by Murakami[23] from the Japanese lichen *Xanthoria fallax*, have been assigned the same structure (XIV), the 7-monomethyl ether of ω-hydroxyemodin (citreorosein); but different melting points were quoted for teloschistin (245-47°) and fallacinol (236-37°). By the partial methylation of ω-hydroxyemodin, a monomethyl ether, m.p. 229-31°, was obtained ;[24] the first reports on teloschistin stated that it melted at 229-30°, and that the m.p. was undepressed by mixing with the 7-monomethyl ether of ω-hydroxyemodin. Both Seshadri and Murakami described the synthesis of (XIV), possessing the same m.p. as natural teloschistin and fallacinol respectively, by the treatment of 4, 5-diacetoxy-7-methoxy-2-bromomethylanthraquinone (XV) with silver acetate or sodium acetate.



(XIV)



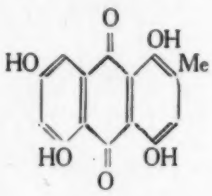
(XV)

Murakami found that fallacinol was accompanied by the corresponding aldehyde, fallacinal, which was subsequently isolated also from *Teloschistes flavicans*.[22]

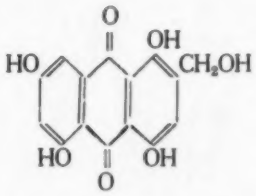
In the synthesis of teloschistin[22], physcion (parietin) diacetate was brominated with *N*-bromosuccinimide (NBS), following the earlier procedure for the conversion of rubiadin to lucidin in which two molecules of the brominating agent were used;[2] (XV) was obtained as a "sticky solid," which was not purified or analysed and was used directly for conversion into teloschistin triacetate. It appears probable that the compound, believed to be (XV), consisted largely of the dibromomethyl derivative, and the ultimate product was the aldehyde, fallacinal, rather than the alcohol (XIV). Murakami[23] used only one molecule of NBS for the bromination of physcion diacetate; he too did not isolate the bromo compound (XV) in the pure state, but treated the crude product with sodium acetate and acetic anhydride, hydrolysed with aqueous sodium hydroxide, and chromatographed a benzene solution of the product on calcium hydrogen phosphate, pretreated with phosphoric acid. Eight bands separated, and fallacinol was recovered from the top band.

The tetra-acetate of natural catenarin (XVI) has been converted by Neelakantan, Pocker and Raistrick to tritisporin (XVII) by the ω-bromination method; the action of NBS on catenarin tetra-acetate yielded a "rather complex mixture of reaction products" from which "a crude

bromoacetate" was isolated; treatment of this bromoacetate with acetic anhydride and sodium acetate gave tritisporin penta-acetate.[25]



(XVI)

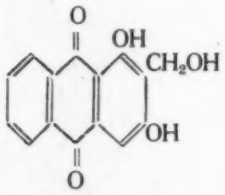


(XVII)

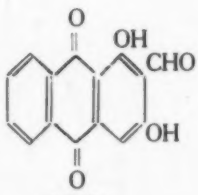
In the NBS method of bromination of 2-methylanthraquinones, not containing acetoxyl groups in both the adjacent positions as in rubiadin diacetate which readily yielded 1, 3-diacetoxy-2-bromomethylanthraquinone,[2] the molar proportion of the brominating agent is important. Ayyangar and Joshi found that, when two molecules of NBS were used for one of 1-acetoxy-3-methylanthraquinone, the product was 1-acetoxy-3-dibromomethylanthraquinone, which was hydrolysed to 1-hydroxyanthraquinone-3-aldehyde by cold sulphuric acid; but when exactly one molecule of NBS was used, the pure monobromo compound was isolable, and treatment with acetic anhydride and sodium acetate gave 1-acetoxy-3-acetoxymethylanthraquinone in good yield. Aloe-emodin was similarly prepared from chrysophanol diacetate.[26]

By the action of formaldehyde in sodium hydroxide solution, xanthopurpurin readily undergoes hydroxymethylation in the 2-position, yielding lucidin (XVIII); lucidin can be oxidised to the aldehyde (XIX) by manganese dioxide in boiling benzene, and to munjistin (the corresponding carboxylic acid) by alkaline silver oxide.[2] The aldehyde (XIX) is of interest because it was subsequently isolated from the heartwood of *Morinda tinctoria*;[27] the 1-monomethyl ether (damnacanthal) accompanies lucidin 1-monomethyl ether (damnacanthol) in the root of *Damnacanthus major*.[28]

Damnacanthol has been synthesised from lucidin via the 2, 3-diacetate and its 1-methyl ether prepared by the action of diazomethane in tetrachloroethane; damnacanthol was then oxidized to damnacanthal by manganese dioxide.[29,30]

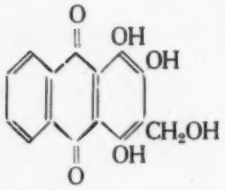


(XVIII)

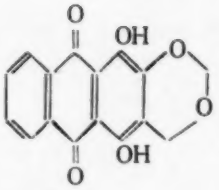


(XIX)

Unlike xanthopurpurin, purpurin gave the corresponding hexahydroxydianthraquinonylmethane, and not the 3-hydroxymethyl derivative (XX), by treatment with formaldehyde and sodium hydroxide solution. The action of formaldehyde and conc. sulphuric acid on purpurin also failed to yield (XX), contrary to Hill and Richter; the product had the properties (analysis, infrared spectrum, alkali -insolubility, formation of diacetate and dimethyl ether) of the 1, 3-dioxan (XXI).[2] 3-Hydroxymethylpurpurin (XX) has now been prepared from 3-methylpurpurin by the ω-bromination method.[26]

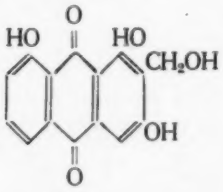


(XX)

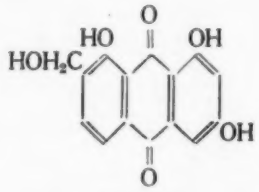


(XXI)

The facile hydroxymethylation of xanthopurpurin to lucidin is useful for the synthesis of analogous anthraquinonylcarbinols and for characterizing 1, 3-dihydroxyanthraquinones, unsubstituted in the 2-position. Hydroxymethylation of 1, 3, 8-trihydroxyanthraquinone gave the 2-hydroxymethyl derivative (XXII),[29] which proved to be different from versicolorin, a colouring matter isolated by Hatsuda and Kuyama[31] from the mycelium of *Aspergillus versicolor*, for which they suggested the alternative structures (XXII) or (XXIII). However, (XXII) has been found to be identical with coelulatin, a pigment isolated from *Coelospermum reticulatum* by R. G. Cooke.[32] In a private communication Dr. Cooke has stated that a point of interest in the constitution of coelulatin is that it occurs in a plant belonging to the family Rubiaceae and "the rule against the occurrence of 1, 8-dihydroxyanthraquinones in this family will now have to be stated in a different form." The isomer (XXIII) has more recently been synthesised by the ω-bromination of 1, 3, 8-triacetoxy-7-methylanthraquinone, replacement of bromine by acetoxyl, and hydrolysis; (XXIII) also did not agree in some of its properties with versicolorin, and the constitution of this pigment therefore needs further investigation.[26]

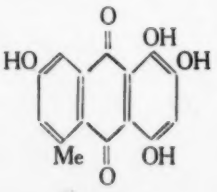


(XXII)

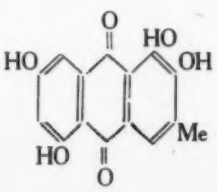


(XXIII)

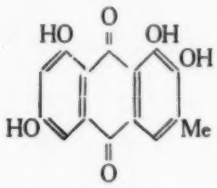
The tentative structure (XXIV) was assigned by Tschirch and Lüdy to erythrolaccin, a yellow pigment isolated from stick-lac.[11] Erythrolaccin has now been shown to be constituted as (XXV),[33] one of the steps in the argument being that it has a xanthopurpurin nucleus unsubstituted in the 2-position because it can be hydroxymethylated by formaldehyde and sodium hydroxide solution; colour reactions, dyeing properties and infrared spectra placed the other two hydroxyls in 1, 2-positions. A choice between (XXV) and (XXVI) was made in favour of (XXV), because of the evidence obtained by Briggs for the structure of alaternin (XXVI), a constituent of the bark of *Rhamnus alaternus*.



(XXIV)



(XXV)

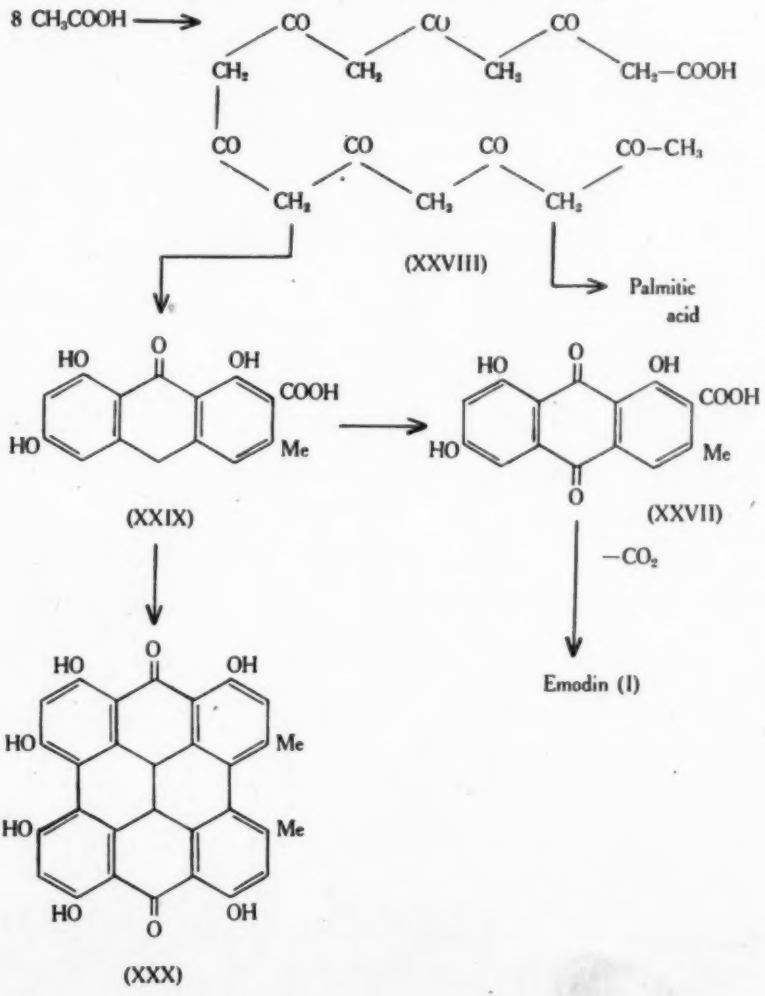


(XXVI)

Attempts are in progress to synthesise rhodocladonic acid by an application of the hydroxymethylation and oxidation methods which led to lucidin and munjistin from xanthopurpurin.

CHART III

Biogenesis of Endocrocin, Emodin and Hypericin.[34]



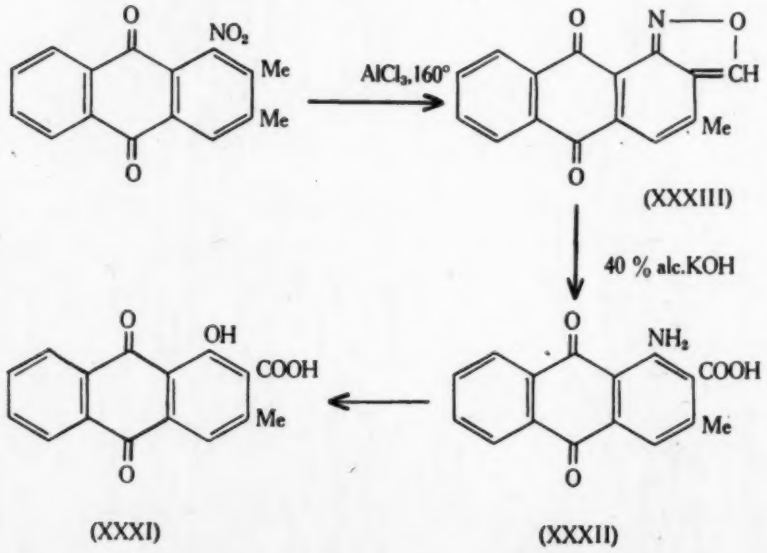
Anthraquinone carboxylic acids are of special interest as likely intermediates in the biogenesis of emodin and other hydroxy-2-methylanthraquinones. Endocrocin (XXVII) in particular occupies a key position, since it can be derived from eight molecules of acetic acid through the heptaketopalmitic acid (XXVIII) as suggested by Robinson, [34] who has also drawn attention to the possibility of the anthrone (XXIX) being a precursor of hypericin (XXX), the photodynamic constitutent of *Hypericum perforatum* (Chart III).[35]

Endocrocin (XXVII) is accompanied by physcion (IV) in the lichen *Nephromopsis endocrocea*,[36] and by catenarin (XVI) as a metabolite of *Aspergillus amstelodami*[37]. It has been very recently found to be a product of the ergot fungus (*Claviceps purpurea*),[38] and of an ultraviolet mutant of *Penicillium islandicum* from which emodin (I), catenarin (XVI) and islandicin (VI) were isolated earlier.[39]

Although the structure of endocrocin (XXVII) is based on adequate evidence, its confirmation by synthesis seemed desirable. In order to devise a suitable method for introducing the carboxyl group in the desired position, the synthesis of the unknown 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (XXXI) was first undertaken. The route ultimately followed is shown in Chart IV.[40] The direct conversion of 1-nitro-2, 3-dimethylanthraquinone to the amino-acid (XXXII) by alkali treatment was not feasible.[41] The isoxazole (XXXIII) was prepared by a known method[42] with the object of carrying out a reductive hydrolysis to 1-amino-3-methylanthraquinone-2-aldehyde, following German patents, and then oxidation to the acid (XXXII), but the yields were very poor. The isoxazole was then found to be hydrolysable to the acid (XXXII) in 50-60% yield by heating with 40% alcoholic potassium hydroxide.

CHART IV

Synthesis of 1-Hydroxy-3-methylanthraquinone-2-carboxylic acid.

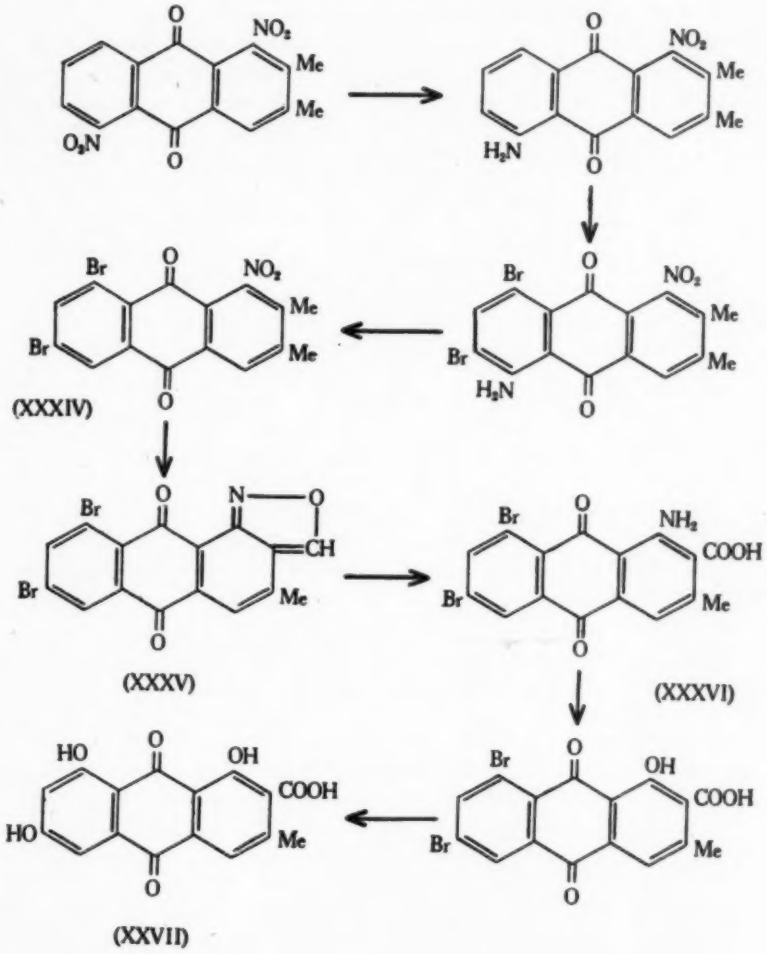


The dinitration of 2, 3-dimethylanthraquinone gave an easily separable mixture of the 1, 5- and 1, 8-dinitro derivatives. An interesting by-product in the nitration, obtained in high yield

by employing suitable conditions, was 1, 4, 5-trinitro-2, 3-dimethylanthraquinone. Starting from 1, 5-dinitro-2, 3-dimethylanthraquinone a synthesis of endocrocin by the reactions outlined in Chart V is in progress.[40]

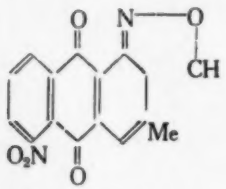
CHART V

A Route to Endocrocin.

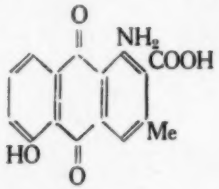


The partial reduction of 1, 5-dinitro-2, 3-dimethylanthraquinone to 1-nitro-5-amino-2, 3-dimethylanthraquinone was effected by the known method of heating with dimethylaniline, and the position of the amino group was confirmed by deamination to 1-nitro-2, 3-dimethylanthraquinone. For the conversion of the nitro compound (XXXIV) to the isoxazole (XXXV) 20% oleum at 25° proved more satisfactory than aluminium chloride at 160°. The hydrolysis of the isoxazole (XXXV) to the amino-acid (XXXVI) presented considerable difficulty. On treatment with 40% alcoholic potash at the reflux for 4 hours, the isoxazole (XXXV) gave (XXXVI) in poor yield,

accompanied by a monobromo compound. Lime under pressure on the corresponding α-hydroxy compound gave a product which, on complete methylation by the potassium carbonate-dimethyl sulphate method, gave an ether-ester melting at 210°, but it did not depress the m.p. of the ether-ester from natural endocrocin, 225-26°, kindly supplied by Professor Shibata. Hydrolysis of (XXXV) with boiling methanolic baryta was found to give a better yield of (XXXVI), but this was again accompanied by the 6-bromo compound. When the mixture was submitted to the usual reactions for replacement of the amino group and the bromine atoms by hydroxyl, the main product appeared to be 1, 6-dihydroxy-3-methylanthraquinone-2-carboxylic acid, since the ultraviolet and visible absorption spectrum resembled that of 1, 6-dihydroxyanthraquinone, rather than endocrocin and emodin, although it exhibited the colour reactions of endocrocin. Improved conditions for the hydrolysis of the isoxazole (XXXV) are being studied, as well as alternative routes involving preferential attack on the 2-methyl group in 1, 5-dinitro-2, 3-dimethylanthraquinone.



(XXXVII)



(XXXVIII)

Another route to endocrocin which was examined was through the isoxazole (XXXVII) obtained in about 20% yield by treatment of 1, 5-dinitro-2, 3-dimethylanthraquinone with oleum; but hydrolysis of the isoxazole with alcoholic potash gave a compound analysing for 1-amino-5-hydroxy-3-methylanthraquinone-2-carboxylic acid (XXXVIII) and not 1-amino-5-nitro-3-methylanthraquinone-2-carboxylic acid. The action of methanolic baryta on (XXXVII) also did not yield the desired product*.

* The infrared spectrum of endocrocin has a band at 1720 cm.$^{-1}$ which is too high for an aromatic carboxylic acid. The possibility that endocrocin is emodin - ω - carboxylic acid has to be considered, and this is now being synthesized.

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STUDIES IN TERPENES. PART VII. A CONTRIBUTION TO THE CHEMISTRY OF TERPINEOL DEHYDRATION

By James Verghese

Earlier researches on the transformations of terpineol with fused potassium hydrogen sulphate, aq. oxalic acid, sulphuric-acetic acid mixture and γ-alumina have been repeated, and in the reaction mixtures, α-terpinene, limonene and saturates have been quantitatively estimated.

Reactions of terpineol, catalysed by iodine and boric acid, have been examined, and iodine has been found to be an excellent and quick agent for dehydrating terpineol.

For eliminating α-terpinene in terpene mixtures, warming with maleic anhydride is shown to be a better route than agitating with cold Beckmann's chromic acid mixture.

Bromination of terpinolene by Baeyer's technique has been improved, the essential change being the precipitation of the tetrabromide by addition of cold methanol. This modification avoids the formation of oily products.

No clean-cut elimination path for terpineol is revealed excepting in dehydrations with potassium hydrogen sulphate and alumina, wherein *dl*-limonene and terpinolene respectively are obtained as major reaction products. In all other cases, there result monocyclics containing α-terpinene, terpinolene, limonene and saturates including *p*-cymene, in varying proportions.

A mechanism is proposed to account for the reaction products and to explain how terpineol can furnish both terpinolene and limonene with equal facility.

Much work has been done on the dehydration of terpineol. Wallach (*Annalen*, 1893, **275,** 103) reported that refluxing terpineol for one hour with fused potassium hydrogen sulphate afforded chiefly dipentene (cf. Flawitsky, *Ber.*, 1887, **20,** 1956; Kremers, *Chem. Zentrl.*, 1909, I, 80, 21; Richter and Wolff, *Ber.*, 1930, **63B,** 1721), while refluxing for half-hour with aq. oxalic acid gave essentially terpinolene (cf. Baeyer, *Ber.*, 1894, **27,** 436; Roberts and Day, *J. Amer. Chem. Soc.*, 1950, **72,** 1226). On increasing the reaction period with aq. oxalic acid to five hours, the alcohol yielded a considerable quantity of α-terpinene, some terpinolene and 1:4-cineole (cf. Goodway and West, *J. Chem. Soc.*, 1940, 702). A more drastic treatment with sulphuric-acetic acid mixture resulted mostly in *p*-cymene and a little α-terpinene (Wallach, *loc. cit.*). It was concluded that the nature of the final products depended on three factors, viz., dehydrating medium, temperature and reaction period.

Further examination of the action of aq. oxalic acid on terpineol has been carried out by other investigators. Dupont *et al.* (*Bull. Soc. Chim.*, 1933, **53,** 393; cf. Booker, *J. Chem. Soc.*, 1940, 1453) found that the crude α-terpinene, separated from the reaction mixture, contained 1:4-cineole (40%), and appreciable amounts of dipentene, terpinolene and α-terpinene. Cineole was determined by complexing with hydroferrocyanic acid, and the other constituents by the Raman spectra (cf. Angus, *Proc. Ind. Acad. Sci.*, 1938, **8A,** 538). On the other hand, Lacrue (*Chem. Zentrl.*, 1942, II, 1795) found that the yield of hydrocarbons increased with longer periods of refluxing and higher oxalic acid concentrations. 1:4-Cineole was estimated by the method of Dupont *et al.* (*loc. cit.*), limonene by interaction with aq. mercuric acetate (cf. Balbiano, *Ber.*, 1915, **48,** 394), and terpinolene by deacetonisation under pressure. Recently Royals ("Advanced Organic Chemistry", Prentice-Hall, Inc., Englewood Cliffs, N. J., 1956, p. 231) indicated that 50% and 10% oxalic acid treatment of terpineol furnished α-terpinene (34%) and 1:4- and 1:8-cineoles (26%) respectively.

Finally, alumina can eliminate water from terpineol. When passed over ordinary alumina at 310-20°, terpineol gave mainly terpinolene (Maihle, *J. usines gaz.*, 1923, **47,** 370; cf. Dupont *et al.*, *loc. cit.*). Other products, recognised in alumina dehydrations, are dipentene, α-and γ-terpinenes (Marot, *Bull. Inst. Pin.*, 1933, **38,** 61) and *p*-cymene (Sondhi *et al.*, this *Journal, Ind. & News Ed.*, 1947, **10,** 28).

In a recent publication, the reaction of terpineol, using the more active γ-alumina, has been reported (Santhanam and Yeddanapalli, *J. Sci. Ind. Res.*, 1959, **18,** 328). Thus the catalysate obtained at 400° included α-terpinene (9%), terpinolene (23%) and *p*-cymene (8%), these percentages being calculated from the yield of the nitrosite, tetrabromide and terephthalic acid respectively. No other hydrocarbons could be detected in the reaction mixture.

The object of the present study is two-fold: (1) to re-investigate the transformations of terpineol (*a*) in the liquid phase, using fused potassium hydrogen sulphate, aq. oxalic acid and sulphuric-acetic acid mixture, and (*b*) in the vapour phase, over γ-alumina, and (2) to examine the behaviour of terpineol towards iodine and boric acid, with a view to clarifying and estimating the reaction products, and to propose a reaction mechanism.

EXPERIMENTAL

A technical grade terpineol was rectified, and the portion with b.p. 217.5-18.5°/760 mm, 148-49°/100 mm, n_D^{30} 1.4780 and d_{25}^{25} 0.9314 was used in these studies.

Oxalic, acetic, sulphuric and boric acids were of analytical grade, and potassium hydrogen sulphate, iodine and maleic anhydride were of chemically pure grade.

γ-Alumina catalyst was prepared by precipitation of the hydroxide from an aq. solution of potassium aluminate as recommended by Eischens and Selwood (*J. Amer. Chem. Soc.*, 1948, **70,** 2271).

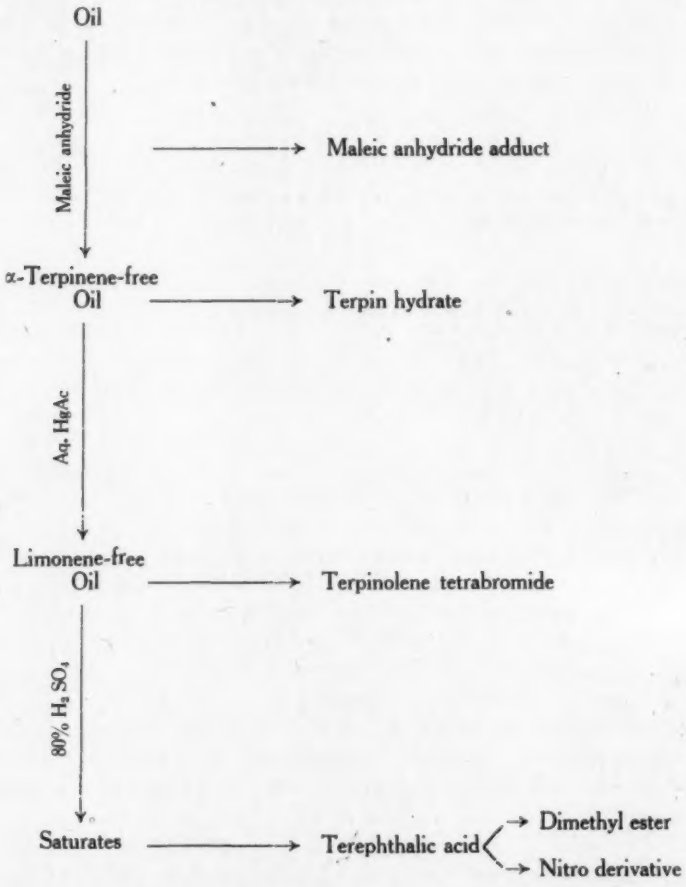
The catalytic unit employed in the gas phase reaction was of the conventional type described earlier (Verghese and Kuriacose, *J. Sci. Ind. Res.*, 1959, **18,** 364).

Reaction.—In general, the liquid phase reactions were carried out by heating terpineol under reflux with the dehydrating agent in question, except for iodine and boric acid reactions; in these cases, the reactants were subjected to slow distillation using a short Quickfit fractionating column. Reaction products were purified by steam distillation, dried over anhydrous magnesium sulphate and analysed.

The gas phase reaction was conducted at 400°, and at a liquid hourly space velocity, *i.e.*, the volume in c.c. of terpineol passed per c.c. of γ-alumina, (LHSV), of 0.34, and collecting the catalysate in a cooled receiver. The organic layer was separated, dried over anhydrous magnesium sulphate and analysed.

Analysis.—Estimation of α-terpinene was made by maleic anhydride addition (Verghese and Samson, *ibid.*, 1959, **18,** 410), limonene by complexing with mercuric acetate (Lacrue, *loc. cit.*), and saturates by agitating with cold 80% sulphuric acid (Verghese *et al.*, *J. Sci. Ind. Res.*, 1953, **12,** 112).

Identification of α-terpinene was *via* the maleic anhydride adduct, m.p. and mixed m.p 64-65° (cf. Ipatieff and Pines, *J. Amer. Chem. Soc.* 1945, **67,** 1227), limonene by conversion to terpin hydrate, m.p. and mixed m.p. 118° (Bhushan *et al.*, this *Journal, Ind. & News Ed.*, 1944, **7,** 62), and p-cymene in all samples of the saturates by oxidation to terephthalic acid (Leo *et al.*, *Curr. Sci.*, 1953, **22,** 112), and further conversion into dimethyl ester, m.p. and mixed m.p. 140-41° (Huntress and Mulliken, "Identification of Pure Organic Compounds, Order I", Chapman & Hall Ltd., Lond., 1946, p. 178) and into nitro derivative, m.p. and mixed m.p. 269° (Lange and Teranish, *J. Chem. Ed.*, 1955, **32,** 40). Terpinolene was recognised by the preparation of the tetrabromide, m.p. and mixed m.p. 116°, utilising a modification of the method of Baeyer (*Ber.*, 1894, **27,** 436) thus : Chilled in ice-salt, a mixture of the oil (1g.), amyl alcohol (1g.) and ether (2g.), and bromine was added dropwise to coloration. Addition of cold methanol precipitated the tetrabromide. The crude product was thrice precipitated from chloroform with methanol. The general scheme of analysis is summarised below :



Results for the transformations of terpineol in the liquid and gas phases are presented in Table I.

TABLE I

Transformations of terpineol.

Expt. No.	Terpineol.	Dehydrating agent.	Temp.	Period.	Analysis of monocyclics.						
					%Yield.	B.P./750 mm.	n_D^{30}.	α-Terpinene.	Limonene.	Saturates.	Terpinolene.
1.	25 g.	Fused potassium hydrogen sulphate 50 g.	180-90°*	1 hr.	80	173-87°	1.4758	15%	63%	5.0%	+
2.	40	Oxalic acid, 120 g. Water, 240 g.	105-10°	5 hrs.	81	173-89°	1.4780	34	20	8.5	+
3.	20	Oxalic acid, 20 g. Water, 40 g.	105-10°	½ hr.	34	175-90°	1.4717	17	43	..	+
4.	30	Sulphuric acid, 2 g. Water, 4 g. Acetic acid, 100 c.c.	95-100°*	7 hrs.	11	173-80°	1.4724	3	Traces	48	..
5.	40	Few crystals of iodine	Distilled	½ hr.	70	173-84°	1.4727	44	33	13	+
6.	25	Boric acid, 10 g.	Distilled	2 hrs.	76	173-89°	1.4747	42	29	..	+
7.	19.5	γ-Alumina, 15.15 g.	400°	(LHSV. 0.34)	83	173-89°	1.4775	15	9	10	+

* Bath temperature.

Column 2 records the amount of terpineol used, and column 3, the dehydrating medium. Temperature and reaction periods are shown in columns 4 and 5 respectively. Yields of monocyclics on the weight of terpineol used and their physical characteristics are recorded in columns 6 to 8. The next three columns record the respective percentages of α-terpinene, limonene and saturates on the weight of the monocyclics; the + sign under the column headed terpinolene indicates the recognition of this hydrocarbon by tetrabromide preparation.

Discussion

With fused potassium hydrogen sulphate, terpineol afforded 80% monocyclics. Dipentene constituted 63% of the monocyclics. Specificity claimed for this material to change terpineol completely to dipentene is untenable. There was the simultaneous formation of 15% α-terpinene, 5% saturates including *p*-cymene, and terpinolene. By difference, terpinolene should not exceed 17%. This assessment does not take into account the possible presence of γ-terpinene, *p*-menthene and *p*-menthane as reaction products. Richter and Wolff (*loc. cit.*) isolated by rigorous fractionation of crude dipentene, obtained by dehydration of terpineol with fused potassium hydrogen sulphate, about 12% of a cut, b.p. 71°/15 mm, which furnished the tetrabromide, m.p. 116°, corresponding to that of terpinolene. This observation is now confirmed by a different technique; the percentage of terpinolene, although approximate, agrees fairly well with that arrived at by earlier investigators. Attention may be drawn to the fact that if potassium hydrogen sulphate is not fused properly, an increase in the α-terpinene content is noticed at the expense of dipentene.

Five hours' refluxing of terpineol with aq. oxalic acid (Expt. 2) yielded 81% monocyclics; this contained 34% α-terpinene, 20% limonene, 8.5% saturates and terpinolene. Although Wallach (*loc. cit.*) reported extensive conversion to α-terpinene on the basis of the nitrosite yield, the maleic anhydride addition technique revealed the α-terpinene content to be 34% (cf. Royals, *loc. cit.*). Other novel findings are the identification of limonene and *p*-cymene as additional reaction products. On the other hand, half-hour's refluxing (Expt. 3), which is a standard method for terpinolene production, furnished only 34% monocyclics besides terpinolene; this included α-terpinene (17%), limonene (43%) and probably cineoles. Thus, even such a mild processing results in a mixture of *p*-menthadienes, difficult to be separated by fractionation (cf. Mosher, *J. Amer. Chem. Soc.*, 1947, **69,** 2140). So, it is now suggested, that prior to tapping terpinolene, the monocyclics should be subjected to successive extractions with maleic anhydride, aq. mercuric acetate, hydroferrocyanic acid, and cold Beckmann's chromic acid mixture (cf. Richter and Wolff, *Ber.*, 1927, **60,** 477), in order to eliminate respectively α-terpinene, limonene, 1: 4-cineole, and γ-terpinene, if any.

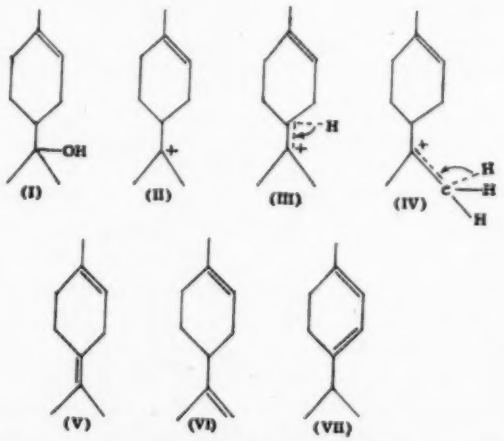
In contrast to the above experiments, with acetic-sulphuric acid mixture (Expt. 4), a sharp fall in monocyclics is observed (yield, 11%). As has been indicated by Wallach (*loc cit.*), negligible quantity of α-terpinene (3%) and a high proportion of saturates (48%), including *p*-cymene, are found in the reaction mixture. From the refractive index of the saturates, n_D^{20} 1.4839, it is to be inferred that *p*-menthane is also present in the oil, but due to the limited quantity of the material, no attempt has been made to isolate this hydrocarbon. The presence of traces of limonene could be recognised by the formation of a very small amount of the mercuric acetate complex.

Findings with iodine (cf. Hibert, *J. Amer. Chem. Soc.*, 1915, **37,** 1748) and boric acid (cf. Bradenberg and Galt, *ibid.*, 1950, **72,** 3275; O'Connor and Nace, *ibid.*, 1955, **77,** 1578) are really

interesting. The technique of dehydration is simple, *i.e.*, slow distillation of terpineol with the catalyst. Without taking into account the pot residues, conversions to monocyclics with iodine and boric acid amounted to 70% and 76% respectively. In both cases, α-terpinene, limonene and terpinolene were identified as reaction products. With iodine, the dehydration was accompanied by *p*-cymene formation, and only a meagre yield of terpinolene (⩾10%) was obtained. Of the two catalysts, iodine seems to be the quicker and better for dehydrating terpineol.

Lastly, the gas phase reaction of terpineol over γ-alumina afforded α-terpinene, terpinolene, limonene and *p*-cymene. Santhanam and Yeddanapalli (*loc. cit.*), on the basis of the nitrosite yield, roughly calculated the α-terpinene content to be 9%, but now, by maleic anhydride addition, this conjugated diene is shown to amount to 15%. Further, the decomposition of α-terpinene by agitation with cold Beckmann's chromic acid mixture is tedious and erratic as the reagent is prone to attack other dienes (Baeyer, *Ber.*, 1894, **27**, 810 ; Guenther, "The Essential Oils", D. Van Nostrand Company, Inc., N.Y., 1952, Vol. II, p. 37 ; Verghese *et al.*, *J. Sci. Ind. Res.*, 1957, **16A**, 530 ; Henry and Paget, *J. Chem. Soc.*, 1921, **117**, 1717 ; 1931, 26, 29). As is shown now, the same objective can be achieved in a better and cleaner way with maleic anhydride (cf. Gasgoine, *J. Proc. Soc., N. S. Wales*, 1941, **74**, 353, 359). Percentages of α-terpinene-free oil arrived at by treatment with Beckmann's chromic acid mixture and maleic anhydride are 76 and 85 respectively. It is noteworthy that the presence of limonene has been established by hydroxylation to terpin hydrate, and estimated by mercuric acetate method (9%).

Calculating the same way as in the potassium hydrogen sulphate reaction, the vapour phase reaction affords about 66% terpinolene. Evidently then, the exo double bond in terpinolene resists migration even at 400° in presence of γ-alumina.



Reaction Mechanism.—Of great interest is the structure and orientation in elimination reactions of terpineol (I). Two primary products are available, viz., terpinolene (V) and limonene (VI). Dehydration leading to terpinolene is in conformity with Satzevy's rule which states that the elimination proceeds in such a manner as to lose tertiary hydrogen in preference to that of primary or secondary (*Annalen*, 1875, **179**, 300). This can be rationalised on the basis of hyperconjugative stabilisation of the transition state for the ejection of a proton from the intermediate carbonium ion (II), which can originate from terpineol by the action of hydrogen ion, iodine or alumina (Whit-

more, *J. Amer. Chem. Soc.*, 1932, **54,** 3274; *Chem. Eng. News*, 1948, **2,** 93; Wheland, "Advanced Organic Chemistry", 2nd ed., John Wiley & Sons, Inc., London., 1951, p. 489; Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37,** 657; Dhar *et al.*, *J. Chem. Soc.*, 1948, 2093). Structure (III) represents most simply the transition state; the dotted lines indicate bonds partially formed or broken. Stabilisation of the incipient double bond by hyperconjugative mesomeric interaction with two methyl groups lowers the energy for expulsion of a proton, leading to terpinolene. On the other hand, the transition state represented by structure (IV) is stabilised by only one methyl group. Proton elimination from this, involving primary hydrogen, affords the least alkylated *p*-diene, limonene (cf. Ingold, "Structure & Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N. Y., 1953, p. 427; Brown *et al.*, *J. Amer. Chem. Soc.*, 1954, **76,** 467; Brown, *J. Org. Chem.*, 1957, **22,** 439; Turner and Garner, *J. Amer. Chem. Soc.*, 1958, **80,** 1424). How this reaction can compete with terpinolene production will be dealt with later.

There is no clear-cut elimination path except in reactions with potassium hydrogen sulphate and alumina; the major single product in these two reactions are 63% *dl*-limonene and 66% terpinolene respectively. In other cases, a mixture of *p*-menthadienes, viz., α-terpinene, terpinolene and limonene with saturates containing *p*-cymene, is obtained. The question naturally arises as to whether limonene or terpinolene is the primary reaction product from terpineol. This can only be answered by ascertaining whether limonene can rearrange to terpinolene and *vice versa* under the experimental conditions. Investigations are in progress in this laboratory to settle this point.

A common feature of almost all reactions under consideration is the formation of α-terpinene (VII) and *p*-cymene. α-Terpinene arises from C_8-ion (II) by a two-step process, viz., rearrangement by hydride ion shift and then expulsion of proton (Verghese *et al.*, *J. Sci. Ind. Res.*, 1957, **16B,** 363), and this conjugated terpene is the most stable of the *p*-menthadienes to which all others converge (cf. Francesoni and Sernagiotto, *Gazzetta*, 1914, **44,** 456). As regards *p*-cymene, it can only originate as a consequence of hydrogen transfer reactions, fulfilling the prediction of Ipatieff and Pines (*loc. cit.*; Verghese, this *Journal*, 1959, **36,** 155; Verghese *et al.*, *loc. cit.*).

Lastly, we have to explain how the same organic entity (II) can yield terpinolene and limonene with equal facility. As has been pointed out before, the formation of terpinolene is to be expected on the basis of the maximum stabilisation of the incipient double bond of the transition state, and for expulsion of a proton only one hydrogen is available. Whereas for limonene formation, six hydrogens are available for a proton expulsion; this reaction can therefore compete with the energetically favoured ejection of a proton involving the tertiary hydrogen. What circumstances dictate the two modes of elimination cannot be said with certainty.

The author wishes to thank Prof. Dr. S. C. Devadatta, Head of the Dept. of Chemistry, Christian Medical College, Vellore, for interest in the work and for permission to publish the results. Also his thanks are due to Rev. Fr. Dr. Lourdu M. Yeddanapalli, S. J., Head of the Dept. of Chemistry, Loyola College, Madras, for permission to incorporate in this publication the results of the γ-alumina catalysed transformations of terpineol done in his laboratory.

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POLYCYCLIC SYSTEMS. PART VII. STUDIES IN THE FORMATION OF ARYL-*CYCLO*HEXENONE DERIVATIVES BY THE ROBINSON-MANNICH BASE SYNTHESIS

BY MAYA GUHA, USHA RAKSHIT AND D. NASIPURI

The Michael-type reaction using the methiodide of aryl β-dimethylaminoalkyl ketones and a few β-oxoesters, e.g., dimethyl β-oxoadipate, its α-methyl derivative and β-oxopimelate have been studied in details. Several *p*-anisyl-*cyclo*hexenones (e.g., VII & VIII) have been synthesised with a view to their possible synthetic uses in the steroidal sex-hormones. The reaction of 4-diethylaminobutan-2-one methiodide with methyl α-methyl-β-oxoadipate (Robinson and Seijo, *J. Chem. Soc.*, 1941, 582) has been reinvestigated.

All these reactions afford interesting observation regarding the *trans*-esterification of the intermediate aldolate ion

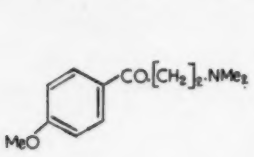
In Parts II and VI of this series (Nasipuri *et al.*, *J. Chem. Soc.*, 1958, 2734; 1960, 1571) a method has been described for the synthesis of hydrochrysene and hydrophenanthrene derivatives by the application of the Robinson-Mannich base synthesis (du Feu, McQuillin and Robinson, *ibid.*, 1937, 53) to aryl methyl ketones. The reaction which consists in the Michael-type condensation of the methiodide of β-dimethylaminoethyl aryl ketones with methyl β-oxoadipate, affords in a single step and in excellent yield, 2-aryl-6-oxo*cyclo*hex-1-enyl acetate or derivatives (e.g., VIII). In the present communication, we wish to record the results of some further extensions of this reaction leading to the synthesis of compounds (VII : R=H, Me) with the ring-carbomethoxyl group in tact, thus permitting further elaboration of the system to that of steroidal hormones by more or less standard methods (cf. Johnson *et al.*, *J. Amer. Chem. Soc.*, 1957, **79**, 1995).

4-Methoxyacetophenone, prepared according to the new method of Dominguez *et al.* (*ibid.*, 1954, **76**, 5150) was converted into β-dimethylamino-*p*-methoxypropiophenone (I) by the usual Mannich reaction. The methiodide was then condensed with dimethyl β-oxoadipate (II : R=H ; n=2) in presence of methanolic potassium methoxide. The product afforded an acidic fraction, m.p. 168°, identified as 2-*p*-anisyl-5-carbomethoxy-6-oxo*cyclo*hex-1-enylacetic acid (VII : R=H) (Turner, *ibid.*, 1951, **73**, 1284 ; Johnson *et al.*, *loc. cit.*) in about 60% yield. A similar reaction of the methiodide with methyl α-methyl-β-oxoadipate (II : R=Me ; n=2) furnished the acid-ester (VII : R=Me), m.p. 130° (Johnson *et al.*, *loc. cit.*) in 42% yield. The latter reaction furnished, in addition, a neutral fraction from which methyl 2-*p*-anisyl-5-methyl-6-oxo*cyclo*hex-1-enylacetate (VIII : R=Me), m.p. 68°, was isolated in 35-37% yield.

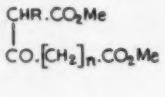
The acid-esters (VII : R=H, Me) were hydrolysed and re-esterified to respective methyl *cyclo*hexenone-acetates (VIII : R=H, Me), the former being previously prepared by Turner (*loc. cit.*) in a different route.

The formation of these acid-esters in the reaction is rather interesting, but not quite unexpected. The initial product of the Michael addition is the dioxo-ester (III) which then forms an aldol. The resultant anion of the aldol (IV) can undergo intramolecular *trans*-esterification in two ways : either (*a*) with the acetic acid side-chain forming the γ-lactone (V), or (*b*) with the ring-carbomethoxyl group giving rise to the bridged δ-lactone (VI). Between these two, the first alternative is obviously preferred and the product (V) on base-catalysed ring-opening furnishes

the acid-ester (VII). The 1:4-lactone structure (VI), on the other hand, will undergo base-catalysed ring-opening with simultaneous decarboxylation, giving rise to the neutral ester (VIII).



(I)



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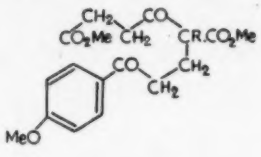

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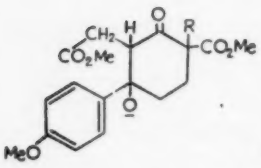

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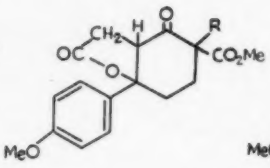

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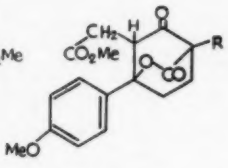

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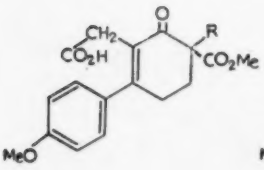
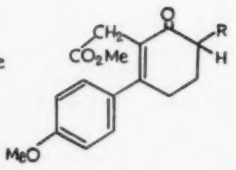
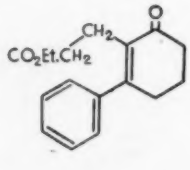


(VII)



(VIII)



(IX)

Examples of such extensive decarbalkoxylation in aldolate ion having a carbalkoxyl group appropriately situated for *trans*-esterification are already in record (Novello *et al.*, *ibid.*, 1953, **75,** 1330; Logan *et al.*, *ibid.*, 1954, **76,** 4127; Horning *et al.*, "Org. Syntheses", 1947, Vol. 27, p. 27). The presence of the acetate side-chain in the present case, thus, has a protecting influence on the ring-carbomethoxyl group, providing an alternative and easier way of *trans*-esterification.

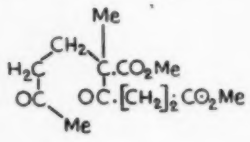
It is interesting to observe that in the condensation with methyl α-methyl-β-oxoadipate, a substantial amount (about 35%) of aldol undergoes 1:4-*trans*-esterification, as evident from the isolation of the neutral decarbomethoxylated ester (VIII : R=Me) directly from the reaction mixture. Reaction with unsubstituted methyl β-oxoadipate, on the other hand, afforded no such decarboxylated product. The reason for this differential behaviour is, however, not quite apparent.

In order to study this point further, ethyl β-oxopimelate (as II : R=H ; n=3), prepared by the ammonolysis of ethyl 2:4-dioxoheptane-1:5-dicarboxylate (Bardhan and Nasipuri, *J. Chem. Soc.*, 1956, 350) was used instead of methyl β-oxoadipate, in the condensation with the methiodide of β-dimethylaminopropiophenone (Vogel, "Practical Organic Chemistry", 3rd ed., p. 911). No acidic fraction, however, could be isolated from the reaction mixture, the sole product being ethyl

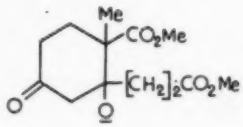
β-2-phenyl-6-oxo*cyclo*hex-1-enylpropionate (IX), isolated in 50% yield. Obviously, the intermediate aldolate ion undergoes 1:4-*trans*-esterification exclusively, in preference to the alternative δ-lactone formation with the propionate side-chain, the 5-carbethoxyl group being subsequently eliminated in the base-catalysed ring-opening process.

The substituted propionic acids, obtainable by the above sequence of reactions, provide important starting materials for the synthesis of polycyclic systems with seven-membered ring, a preliminary account of which has already been reported from our laboratory (Guha and Nasipuri, *Science & Culture*, 1960, **25**, 492).

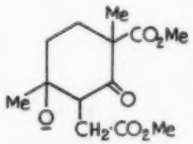
It may be relevant to mention in this connection, the reaction of the methiodide of 4-diethylaminobutan-2-one with methyl α-methyl-β-oxoadipate, carried out by Robinson and Seijo (*J. Chem. Soc.*, 1941, 582) who failed to obtain the desired condensation product (methyl ester of XVI) in any reasonable yield. In the light of the present discussion, it is apparent that the initial Michael addition product (X), on aldol condensation, can give rise to two aldolate ions (XI & XII) which in turn can undergo intramolecular *trans*-esterification in three ways to yield the lactones (XIII, XIV & XV). The first two, on base-catalysed ring-opening, will furnish acidic products (XVI & XVII) and the third (XV) will undergo decarboxylation to furnish a neutral ester



(X)



(XI)



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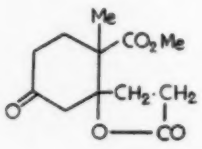

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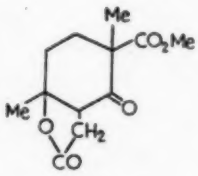
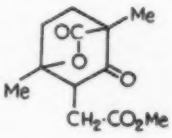
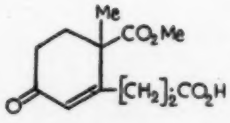


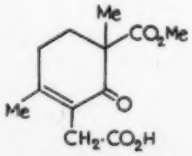
(XIV)



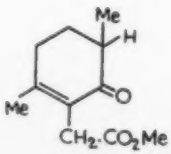
(XV)



(XVI)



(XVII)



(XVIII)

(XVIII). On reinvestigation of this reaction under modified experimental condition, acidic materials were indeed obtained in good yield (70%). The acid could not be induced to crystallise. It was esterified with diazomethane and the ester afforded elemental analysis corresponding to the methyl ester of the acid (XVI or XVII). Further investigations on the structure of the product are in progress.

EXPERIMENTAL

β-Dimethylamino-p-methoxypropiophenone (I).— 4-Methoxyacetophenone required for this purpose was prepared by acetylating anisole with iodine as catalyst according to the method of Dominguez *et al.* (*loc. cit.*). A mixture of 4-methoxyacetophenone (25 g.), dimethylamine hydrochloride (16 g.), paraformaldehyde (6 g.), ethanol (30 c.c.) and HCl (conc., 0.5 c.c.) was refluxed on the water-bath for 4 hrs. After removal of most of the alcohol under reduced pressure, the crystalline hydrochloride was dissolved in minimum quantity of water, extracted with ether to remove any unchanged ketone, and the cooled aqueous solution was basified with 40% KOH solution. The aminoketone was extracted thoroughly with ether, dried (K_2CO_3) and the residue (30 g.), m.p. 32-33°, after evaporation of the solvent was directly used for the preparation of the methiodide.

2-p-Anisyl-5-carbomethoxy-6-oxocyclohex-1-enylacetic Acid (VII : R=H)—The above aminoketone (10.5 g.) was dissolved in dry thiophene-free benzene (50 c.c.), cooled in an ice-bath and methyl iodide (3.6 c.c.) was slowly added with stirring. Stirring was continued for 4 hrs. more at room temperature. To the crystalline methiodide, thus obtained, was added a methanolic solution of potassio derivative of methyl β-oxoadipate, prepared from potassium (2 g.), anhydrous methanol (25 c.c.) and β-oxo-ester (11.3 g.). The whole mass was then stirred at the room temperature until the crystalline methiodide was gradually replaced by granular potassium iodide (2-3 hrs.). A further amount of potassium methoxide, prepared from potassium (1 g.) and methanol (12.5 c.c.), was then added and the mixture refluxed on the water-bath for 4 hrs. It was cooled, decomposed with $2N$-H_2SO_4 and the organic matter taken up in ether. The ethereal solution was extracted with a saturated solution of $NaHCO_3$ till no further acidic material was left in the ethereal layer. The bicarbonate extract was cooled and carefully acidified with HCl (conc.) to provide an oily substance which quickly solidified on scratching. The solid was collected by filtration and dried to furnish the acid-ester (VII : R=H) (9.5 g.), m.p. 150-55°. On several crystallisations from ethyl acetate, it was finally obtained in light yellow prisms, m.p. 168°, λ_{max}^{EtOH} 224 and 300 mμ (log ε 4.08 and 4.10 respectively). (Found : C, 64.0; H, 5.7; equiv., 317. Calc. for $C_{17}H_{18}O_6$: C, 64.1 ; H, 5.6% ; equiv., 318).

The ethereal layer, left after the bicarbonate extract, was washed with water, dried ($MgSO_4$), evaporated and the residue was distilled in high *vacuo* to yield two fractions : Fraction (A), b.p. 120-30°/0.3 mm (1 g.), developed a violet colour with EtOH-$FeCl_3$ solution. It is most probably methyl β-oxoadipate. Fraction (B) (0.8 g.), b.p. 210-30°/0.3mm, was not investigated further.

Methyl 2-p-Anisyl-6-oxocyclohex-1-enylacetate (VIII : R = H).— The preceding half-ester (5 g.) was hydrolysed by boiling in 10% ethanolic KOH solution for 3 hours and the crude acid (3 g.) was crystallised from ethyl acetate and petroleum ether (b.p. 40-60°) in colorless prisms, m.p. 137°. (Found : C, 69.3 ; H, 6.3. Calc. for $C_{15}H_{16}O_4$: C, 69.2 ; H, 6.1%). Turner (*loc. cit.*) reports m.p. 137-138.5°.

It readily furnished a *dinitrophenylhydrazone* which crystallised from benzene-petroleum ether in red needles, m.p. 250-52° (decomp.). (Found : N, 12.9. $C_{21}H_{20}O_7N_4$ requires N, 12.7%).

The methyl ester (VIII : R = H), prepared by boiling in methanolic hydrochloric acid, was obtained as a viscous gum which crystallised from methanol in colorless plates, m.p. 95-96°. (Found : C, 70.2 ; H, 6.5. Calc. for $C_{16}H_{18}O_4$: C, 70.1 ; H, 6.6%). Turner reports m.p. 91° for the methyl ester (*loc. cit.*).

The ester afforded a *dinitrophenylhydrazone*, m.p. 148° (from benzene-methanol). (Found : N, 12.1. $C_{22}H_{22}O_7N_4$ requires N, 12.3%).

2-p-*Anisyl-5-carbomethoxy-5-methyl-6-oxocyclohex-1-enylacetic Acid* (VII : R = Me).— To a cooled suspension of the methiodide of the aminoketone (I) (12.0 g.) in benzene (60 c.c.), prepared as before, was added a solution of potassium (3.9 g.), and methyl α-methyl-β-oxoadipate (12.5 g.) in methanol (50 c.c.). The mixture was stirred at room temperature for 2 hours and then refluxed on the water-bath for an additional period of 4 hours. The product was worked up in the usual way and separated into two fractions as before :

(*A*). The acidic fraction was isolated by $NaHCO_3$-extraction of the ethereal solution and it afforded the acid-ester (VII : R = Me) (8 g., 41.5%) as viscous oil which solidified on keeping. This was crystallised from benzene-petroleum ether and then from ethyl acetate-petroleum ether (40-60°) in colorless plates, m.p. 129°. (Found : C, 65.2 ; H, 6.1 ; equiv., 331. Calc. for $C_{18}H_{20}O_6$: C, 65.1 ; H, 6.0% ; equiv., 332). Johnson *et al.* (*loc. cit.*) report m.p. 129.5-130.5°.

(*B*). The ethereal solution left after $NaHCO_3$-extraction was evaporated and the residue distilled in high *vacuo* to yield (*i*) a low-boiling fraction (1.5 g.), b.p. 105-10°/1 mm, and (*ii*) a high-boiling fraction (6 g.), b.p. 195-210°/1 mm. The latter fraction solidified in the receiver. It was crystallised from benzene-petroleum ether (40-60°) in colorless plates, m.p. 67°. It was found to be identical with methyl 2-*p*-anisyl-5-methyl-6-oxocyclohex-1-enylacetate (VIII : R = Me) (*vide infra*) by mixed m.p. determination and analysis. (Found : C, 70.6 ; H, 6.9. $C_{17}H_{20}O_4$ requires C, 70.8 ; H, 6.9%).

2-p-*Anisyl-5-methyl-6-oxocyclohex-1-enylacetic Acid.*—The acid-ester (VII : R = Me) (6 g.) was hydrolysed by boiling 10% ethanolic KOH solution for 3 hours. The crude *acid* (3.7 g.) was converted directly into the *methyl ester* (VIII : R=Me), m.p. 67° (methanol), by boiling with 5% MeOH-HCl solution. A part of the crystalline ester was hydrolysed with 5% EtOH-KOH solution and the acid on several crystallisations from ethyl acetate-petroleum ether (60-80°) was obtained in glistening prisms, m.p. 142-43°. (Found : C, 70.2 ; H, 6.7% ; equiv., 275. $C_{16}H_{18}O_4$ requires C, 70.1 ; H, 6.6% ; equiv., 274).

Ethyl β-*Oxopimelate* (II : R = H ; $n = 3$).—A stream of dry ammonia gas was passed through a solution of ethyl 4:6-dioxoheptane-1:5-dicarboxylate (30 g.) in dry ether (50 c.c.) for 45 mins., while the solution was kept cooled in a freezing mixture. After the mixture was left overnight, it was decomposed by shaking vigorously with HCl (cold, dilute) and ethyl β-oxopimelate was taken up in ether, dried, and the solvent evaporated. The residue was distilled to yield the β-oxo-ester (14.2 g., 55%), b.p. 120-21°/0.2 mm, n_D^{28} 1.4400. Hunter and Hogg. (*J. Amer. Chem. Soc.*, 1949, **71**, 1924) report b.p. 120-21°/0.15 mm. A good middle fraction was analysed. (Found : C, 57.4 ; H, 8.1. Calc. for $C_{11}H_{18}O_5$: C, 57.4 ; H, 7.8%).

It afforded a *phenylpyrazolone* derivative on being heated with phenylhydrazine. It was crystallised from aqueous ethanol in plates, m.p. 245° (decomp.). (Found : C, 65.4 ; H, 6.7 ; N, 10.4. Calc. for $C_{15}H_{18}O_3N_2$: C, 65.7 ; H, 6.6 ; N, 10.2%). Loewenthan (*J. Chem. Soc.*, 1953, 3962) reports 240° as the m.p. of the phenylpyrazolone derivative.

Ethyl β-*2-Phenyl-6-oxocyclohex-1-enylpropionate* (IX).—The methiodide of β-dimethylaminopropiophenone (9 g.) in dry benzene (25 c.c.) was condensed with ethyl β-oxopimelate (13.6 g.) in presence of ethanolic potassium ethoxide, prepared from potassium (2 g.) and super-dry ethanol (40 c.c.) in the manner described before. When the initial reaction was complete, an additional amount of potassium ethoxide from potassium (1. g.) and ethanol (20 c.c.) was added and the whole refluxed for 4 hrs. The product was worked up in the usual way and the organic matter extracted thoroughly with ether. The ethereal extract was washed with saturated $NaHCO_3$ solution, but no acidic material was obtained. The ethereal solution was evaporated and the residue on distillation afforded the neutral *ester* (IX) (6.8 g., 50%), b.p. 170-72°/0.2 mm as a viscous oil. (Found : C, 75.3 ; H, 7.5. $C_{17}H_{20}O_3$ requires C, 75.0 ; H, 7.3%).

It formed a *dinitrophenylhydrazone*, m.p. 141-42° (from benzene-methanol). (Found : N, 12.6. $C_{23}H_{24}O_6N_4$ requires N, 12.4%).

The corresponding *acid*, obtained by hydrolysis, could not be solidified, but it formed a crystalline semicarbazone, m.p. 238°. (Found : N, 13.7. $C_{16}H_{19}O_3N_3$ requires N, 13.95%).

The *methyl ester*, prepared by heating the acid with MeOH-HCl solution, was obtained as a low-melting solid, m.p. 36° (from petroleum ether, b.p. 40-60°). (Found : C, 74.1 ; H, 7.1. $C_{16}H_{18}O_3$ requires C, 74.4 ; H, 6.9%).

It formed a *dinitrophenylhydrazone*, m.p. 155° (from benzene-methanol). (Found : N, 12.8. $C_{22}H_{22}O_6N_4$ requires N, 12.8%).

Condensation of the Methiodide of 4-*Diethylaminobutan-2-one with Methyl* α-*Methyl-*β-*oxoadipate*—4-Dimethylaminobutan-2-one (7.5 g.), prepared according to Wilds and Shunk (*J. Amer. Chem. Soc.*, 1943, **65,** 469), was converted into its methiodide by addition of methyl iodide (3.8 c.c.), following the technique of Cornforth and Robinson (*J. Chem. Soc.*, 1949, 1855). To this was added a solution of methyl α-methyl-β-oxoadipate (10.5 g.) in dry benzene (50 c.c.), followed by an ethanolic solution of potassium (3.3. g.) in absolute ethanol (50 c.c.). The mixture was shaken at the room temperature for 2 hours and then refluxed on the water-bath for an additional period of 2 hrs. It was then cooled, decomposed with 2*N*-H_2SO_4, and the benzene layer separated. The aqueous layer was once extracted with ether and the combined organic layer was repeatedly washed with $NaHCO_3$ solution. The total bicarbonate extract was then carefully acidified with HCl (conc.) and the precipitated organic matter was taken up in ether, dried (Na_2SO_4) and evaporated to leave a gummy residue (XVI or XVII) (9.1 g., 70%). This was esterified by an ethereal solution of diazomethane and the ester distilled in high *vacuo* to provide a colorless oil, b.p. 155-60°/0.2 mm. (Found : C, 61.4 ; H, 7.4. $C_{13}H_{18}O_5$ requires C, 61.4 ; H, 7.1%).

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STUDIES ON THE DEPENDENCE OF OPTICAL ACTIVITY ON CHEMICAL CONSTITUTION. PART LI. CORRELATION OF THE CHARACTERISTIC WAVE-LENGTHS FROM DRUDE'S ROTATORY DISPERSION EQUATION AND ABSORPTION MAXIMA

By Bawa Kartar Singh and Bhupendra Sahai Saxena

Both, one-term as well as two-term Drude's rotatory dispersion formulae, express equally well the optical rotatory dispersion of the compounds in the visible range (6708 Å-4358 Å). The characteristic wave-lengths (λ_0), derived from these equations, do not agree with the observed ultraviolet absorption maxima. The complex rotatory dispersion equations in some cases are almost equivalent to the one-term simple equations, with the second term contributing practically nothing to rotatory power ; in other cases both terms are significant and the two characteristic wave-lengths obtained in these cases are nearer, but not equal to the absorption bands.

Thus the characteristic wave-lengths calculated from one and two-term rotatory dispersion equations are not the real absorption bands, but only the weighted average of the observed bands and those unobserved in the far ultraviolet.

The method of building up a two-term equation by substituting the two observed absorption maxima in place of two characteristic wave-lengths not only suffers from the defect that some hypothetical bands can be fitted in equally well, but also that it ignores other unobserved ultraviolet bands beyond the working range of the instrument.

The effect of chemical constitution on rotatory power and ultraviolet absorption bands is discussed.

The rotatory dispersion and ultraviolet absorption spectra of camphanoquinoxalines, camphanodihydroquinoxalines, *m*-phenylene-*bis*-imino- and -aminocamphors and *p*-phenylene-*bis*-imino- and -aminocamphors are described.

The rotatory dispersion of an optically active compound can be expressed by Drude's formula :

$$[\alpha]_\lambda = \sum \frac{K}{\lambda^2 - \lambda_0^2}$$

in which the summation covers all the absorption bands, and gives a series of similar terms, e.g.,

$$\frac{K'}{\lambda^2 - \lambda'^2_0}, \quad \frac{K''}{\lambda^2 - \lambda''^2_0}, \quad \frac{K'''}{\lambda^2 - \lambda'''^2_0}$$

where K', K'', K''' etc. represent the rotation constants and each term is associated with an absorption band (wave-length λ_0). The observed rotations of optically active compounds are, in fact, accurately reproduced by expressions of this form, provided that the wave-length, λ, used in measuring specific rotations, $[\alpha]_\lambda$, does not lie in any of the absorption regions of the compounds.

In the present communication we have calculated both one-term as well as two-term rotatory dispersion equations for these compounds in ethyl alcohol to ascertain how far they agree between themselves and with the ultraviolet absorption maxima (λ_{max}) obtained by direct measurements.

Experimental

The compounds studied here were prepared and purified as described earlier (Singh and Saxena, this *Journal*, 1960, **37**, 60).

The specific rotatory powers of the compounds were determined in several solvents at 35° in a 2-decimetre jacketted polarimeter tube for the visible region of the spectrum (6708 Å-4358 Å). Drude's one-term rotatory dispersion equations expressing the rotatory dispersion in this range are recorded in Table I, instead of the observed and calculated specific rotatory powers, to economise space.

TABLE I

Drude's one-term rotatory dispersion formulae.

Compound.		MeOH. [31.5]**	EtOH. [25.8]	Acetone. [21.5]	EtAc. [6.11]	$CHCl_3$. [5.2]	Benzene. [2.28]
1. *d*-Camphanoquinoxaline	$[\alpha]_\lambda^{35°} =$	$\frac{8.607}{\lambda^2-(2893)^2*}$	$\frac{8.592}{\lambda^2-(2849)^2}$	$\frac{8.549}{\lambda^2-(2797)^2}$	$\frac{9.472}{\lambda^2-(2802)^2}$	$\frac{8.171}{\lambda^2-(2736)^2}$	$\frac{9.5102}{\lambda^2-(2901)^2}$
2. *m*-Phenylene-*bis*-imino-*d*-camphor	$[\alpha]_\lambda^{35°} =$	$\frac{119.425}{\lambda^2-(3919)^2}$	$\frac{125.421}{\lambda^2-(3890)^2}$	$\frac{122.380}{\lambda^2-(3939)^2}$	$\frac{118.596}{\lambda^2-(3973)^2}$	$\frac{132.936}{\lambda^2-(3814)^2}$	$\frac{126.188}{\lambda^2-(4031)^2}$
3. *p*-Phenylene-*bis*-imino-*d*-camphor	$[\alpha]_\lambda^{35°} =$	$\frac{197.46}{\lambda^2-(4192)^2}$	$\frac{205.42}{\lambda^2-(4205)^2}$	$\frac{217.16}{\lambda^2-(4217)^2}$	$\frac{221.76}{\lambda^2-(4260)^2}$	$\frac{228.42}{\lambda^2-(4272)^2}$	..
4. *d*-Camphanodihydroquinoxaline	$[\alpha]_\lambda^{35°} =$	$\frac{38.516}{\lambda^2-(3082)^2}$	$\frac{43.105}{\lambda^2-(3013)^2}$	$\frac{52.275}{\lambda^2-(3221)^2}$	$\frac{54.183}{\lambda^2-(3288)^2}$	$\frac{50.842}{\lambda^2-(3298)^2}$	$\frac{59.254}{\lambda^2-(3394)^2}$
5. *m*-Phenylene-*bis*-amino-*d*-camphor	$[\alpha]_\lambda^{35°} =$	$\frac{34.386}{\lambda^2-(2433)^2}$	$\frac{35.052}{\lambda^2-(2545)^2}$	$\frac{39.984}{\lambda^2-(2629)^2}$	$\frac{40.121}{\lambda^2-(2738)^2}$	$\frac{41.340}{\lambda^2-(2815)^2}$	$\frac{38.242}{\lambda^2-(2952)^2}$
6. *p*-Phenylene-*bis*-amino-*d*-camphor	$[\alpha]_\lambda^{35°} =$	$\frac{19.01}{\lambda^2-(3192)^2}$	$\frac{23.85}{\lambda^2-(3185)^2}$	$\frac{31.46}{\lambda^2-(2550)^2}$	..	$\frac{34.51}{\lambda^2-(2578)^2}$	$\frac{32.49}{\lambda^2-(2602)^2}$

* Figures in small brackets are characteristic wave-lengths in Å

** Figures in square brackets are the values of the dielectric constants of the solvent.

TABLE II

Drude's two-term rotatory dispersion formulae in ethyl alcohol.

Compounds :	*d*-Camphanoquinoxaline	*d*-Camphanodihydroquinoxaline	*m*-Phenylene-*bis*-amino-*d*-camphor	*p*-Phenylene-*bis*-amino-*d*-camphor
Conc. (g./100 c.c.):	1.0000	1.0000	1.0000	0.5000
Calc. $[\alpha]_{\lambda}^{35°}$ ..	$\frac{8.5703}{\lambda^2-0.08138} + \frac{0.0152}{\lambda^2-0.1620}$	$\frac{13.6623}{\lambda^2-0.12219} - \frac{30.6237}{\lambda^2-0.06142}$	$\frac{5.0428}{\lambda^2-0.09847} + \frac{30.1802}{\lambda^2-0.05628}$	$\frac{23.7141}{\lambda^2-0.10259} - \frac{0.0104}{\lambda^2-0.49590}$
λ_0 ..	2853 4025	3496 2478	3138 2372	3203 7042

Lines.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
6708	23.5	23.30	—120.5	—120.50	91.0	91.01	68.5	68.50
6438	26.0	25.78	133.0	133.45	100.5	100.19	76.5	76.15
6104	29.5	29.51	153.0	153.00	113.5	113.83	88.0	87.93
5893	32.0	32.32	168.0	167.86	124.0	124.00	97.0	97.00
5780	34.0	34.00	177.5	176.78	130.5	130.03	102.5	102.50
5468	39.5	39.50	206.0	206.21	149.5	149.51	120.5	120.82
5461	39.5	39.64	207.0	206.96	150.0	150.00	121.5	121.29
5209	45.5	45.25	239.0	237.48	169.5	169.50	141.0	140.58
5086	48.5	48.50	255.0	255.37	180.5	180.61	152.0	152.00
4800	58.0	57.73	307.5	307.50	211.5	211.56	185.0	185.60
4678	62.5	62.61	336.0	335.85	227.5	227.53	204.0	204.01
4603	66.0	66.00	356.0	356.00	238.5	238.50	216.0	217.13
4358	79.5	79.48	..	..	280.0	280.89	271.5	271.50

TABLE III

Absorption maxima (λ_{max}) and characteristic wave-lengths (λ_0) in ethyl alcohol.

S. No.	Compound.	Conc. (g./100 c.c.).		Dextro isomer.		Racemic isomer.		λ_0 from Drude's equation.	
		Dextro.	Racemic.	$\lambda_{max.}$	$\epsilon_{max.}$	$\lambda_{max.}$	$\epsilon_{max.}$	One-term.	Two-term.
1.	Camphanoquinoxaline	0.004	0.004	315mμ 241	10371 24250	315mμ 242	11333 26020	284.9mμ	402.5mμ 285.3
2.	*m*-Phenylene-*bis*-iminocamphor	0.003	0.003	324 224	8094 29358	324 224	7286 27607	389.0	..
3.	*p*-Phenylene-*bis*-iminocamphor	0.002	0.003	347 228 208	11730 20604 23562	348 228 209	11380 19931 21143	420.5	..
4.	Camphanodihydroquinoxaline	0.002	0.002	343 232	4380 49680	344 232	4300 48502	301.3	349.6 247.8
5.	*m*-Phenylene-*bis*-aminocamphor	0.003	0.002	303 228	3726 27608	303 226	3458 25847	254.5	313.8 237.2
6.	*p*-Phenylene-*bis*-aminocamphor	0.002	0.00.2	323 256	3366 22114	323 255	3505 24142	318.5	704.2 320.3

	$\lambda_{max.}$	$\epsilon_{max.}$		$\lambda_{max.}$	$\epsilon_{max.}$
Phenyliminocamphor*	324 226	2318 8395	Phenylaminocamphors	*298 248 211	1985 10530 5856

* Singh and Saxena, this *Journal*, *loc. cit.*

The absorption measurements were taken in very dilute solutions of the substances in spectroscopically pure ethyl alcohol with a Beckman DU spectrophotometer up to the lowest limit (208 mμ) of the instrument. The absorption curves were plotted between wave-length and molecular extinction coefficients. Only a few of the curves (Figs. 1 and 2) have been given as illustration. The absorption maxima (λ_{max}) have been tabulated (Table III) along with characteristic wave-lengths (λ_0), obtained from one-term and two-term Drude's equations for comparison.

DISCUSSION

The rotatory dispersion of all these compounds, when plotted between reciprocal of specific rotatory power $1/[\alpha]_\lambda$ and square of wave-length (λ^2), furnishes straight lines and can be expressed very well by Drude's one-term formula $[\alpha]_\lambda = \frac{K}{\lambda^2 - \lambda_0^2}$. The formulae for each of these compounds in several solvents have been recorded in Table I. There is a good agreement between the observed values of specific rotatory powers and those calculated from one-term Drude's rotatory dispersion equation. The differences are within the experimental error corresponding to a maximum difference of 0.02° in the observed angle of rotation. The *characteristic* wave-lengths (λ_0), which may be expected to be equal to the selective absorption bands, (λ_{max}), of the compound, do not agree with any of the absorption bands obtained by direct measurements (Table III). These are thus not the actual absorption bands, but probably represent the weighted average of all the ultraviolet absorption bands.

d-Camphanoquinoxaline, *d*-camphanodihydroquinoxaline, *m*- and *p*-phenylene-*bis*-amino-*d*-camphors show two absorption maxima in the ultraviolet (between 400 mμ and 208 mμ) in ethyl alcohol (Table III). The two-term Drude's rotatory dispersion equation in the case of these compounds may therefore be expected to provide characteristic wave-lengths λ'_0 and λ''_0 equal to the two absorption maxima. These two-term rotatory dispersion formulae in ethyl alcohol are recorded in Table II. The values of specific rotatory power, calculated from these complex dispersion formulae, agree equally well with the observed values (Table II) as in the case of one-term formulae.

In the case of *d*-camphanoquinoxaline and *p*-phenylene-*bis*-amino-*d*-camphor it is found (Table II) that out of the two characteristic wave-lengths, one is almost equal to the characteristic wave-length of the one-term formula (Table I), while the other is high and the contribution of the partial rotation term containing it, to the rotation, is practically negligible. Thus, the two-term equations in these cases are reduced to one-term.

In the case of *m*-phenylene-*bis*-amino-*d*-camphor and *d*-camphanodihydroquinoxaline, however, both the characteristic wave-lengths of the two-term formulae also differ from the corresponding absorption maxima but by fewer units than do the characteristic wave-lengths from one-term formulae (Table III). These differences may be due to the fact that the two-term equation furnishes two characteristic wave-lengths, λ'_0 and λ''_0, which are probably the weighted average of the two absorption maxima (λ_{max_1}, λ_{max_2}) observed in the spectral range, 400-208 mμ (208 mμ being the lower wave-length limit of the Beckman DU spectrophotometer) and other bands farther in the ultraviolet which have not been observed.

We have found similar divergences between the values of λ_0 and λ_{max} in other series of compounds (unpublished work).

Lowry and Hudson (*Phil. Trans.*, 1934, **A232**, 117) found, in the case of optically active xanthates, definite divergences between absorption maxima and the characteristic wave-lengths calculated from the two-term rotatory dispersion equation.

The fact that the characteristic wave-length calculated from the one-term Drude's equation differs more from the absorption bands while a two-term formula provides the two characteristic wave-lengths, which are closer to the real absorption bands, shows that the two-term equation is definitely a step in advance, but that some more terms in Drude's equation corresponding to the remaining unobserved ultraviolet absorption bands (below 208 mμ) are required for an exact agreement between λ_{max} and λ_0s.

The two-term formula of rotatory dispersion, containing four constants, would require four simultaneous equations for the evaluation of these constants. The calculations of the λ_0s from two (or more)-term equations being somewhat tedious algebraic operations, these have thus been generally avoided by chemists.

Recently Vasistha and Sarma (this *Journal*, 1959, **36**, 549) determined the rotatory dispersion of some aryl camphor-β-sulphonates and found that it could be expressed by Drude's *one-term* equation. They state that it can also be expressed equally well by a *two-term* equation,

$$[\alpha]_\lambda = \frac{K'}{\lambda^2 - \lambda_0'^2} \pm \frac{K''}{\lambda^2 - \lambda_0''^2},$$

when the two absorption maxima, λ_{max_1}, λ_{max_2} (observed within the range 400 mμ −208 mμ) are substituted for λ'_0 and λ''_0. This method of treatment based on substitution is obviously erroneous; some arbitrary wave-lengths, other than the absorption maxima λ_{max_1}, λ_{max_2} can also satisfy the equation, so that there is an agreement between the observed and calculated values of rotatory power. The argument based on substitution of absorption maxima for characteristic wave-length, thus, militates against this treatment. Moreover, there are very probably other absorption maxima farther in the ultraviolet (*i.e.*, lower than 208 mμ) which cannot be observed with a Beckman DU spectrophotometer.

The correct rotatory dispersion equation covering all the ultraviolet absorption bands can only be evaluated if we know all the absorption bands, and not by substitution of a few bands registered by the instrument; bands below 208 mμ must also be taken into account.

The above mentioned treatment of these authors, which does not take into account all the ultraviolet absorption bands in the building up of Drude's equation for rotatory dispersion, is thus incorrect.

Chemical Constitution and Ultraviolet Absorption Spectra

The effect of conjugation and insulation of chromophores, as observed by Gillam and Hey (*J. Chem. Soc.*, 1939, 1170) in the case of polyphenyls and by Ferguson and Branch (*J. Amer. Chem. Soc.*, 1944, **66**, 1467) in the case of some aromatic imino compounds, is strikingly revealed by the absorption spectra of *m*- and *p*-phenylene-*bis*-iminocamphors in relation to phenyliminocamphor. The two bands at 324 mμ and 226 mμ of phenyliminocamphors (Singh and Saxena, *loc. cit.*) remain unchanged, as regards wave-length, in the case of *m*-phenylene-*bis*-iminocamphors with two insulated chromophoric systems, but the intensity of light absorption of both the bands is much increased (Table III). In *p*-phenylene-*bis*-iminocamphors (Table III), due to the same two chromophores being in conjugation, the 324 mμ band is shifted by 23 mμ towards longer wave-lengths and with much higher intensity. Such a remarkable shift is, however, not shown by the second band. The *para* isomer shows a third very strong band (208-209 mμ) which is found to occur in some phenyliminocamphor derivatives.

Phenylene-*bis*-aminocamphors (*m*- and *p*-) show two bands which correspond with the absorption maxima of the bases determined by us :

	$\lambda_{max.}$	$\epsilon_{max.}$
m-Phenylenediamine ..	294 mμ	923
	216	8154
p-Phenylenediamine ..	312 mμ	1123
	244	4158

These have, however, shifted towards longer wave-lengths by 9-12 mμ in the case of these compounds and have much higher extinction coefficients.

Camphanoquinoxalines show two bands at 315 mμ and 241 mμ. The former is due to the pyrazine ring (Allan, *J. Chem. Soc.*, 1946, 670). Both these bands of camphanoquinoxalines are markedly changed by the partial reduction of the compound to camphanodihydroquinoxaline (Table III).

Effect of Chemical Constitution on Rotatory Power

The rotatory power of *para* isomer is generally higher than that of the *meta* as in the case of *m*- and *p*-phenylene-*bis*-iminocamphors. This order is, however, reversed in the case of

FIG. 1

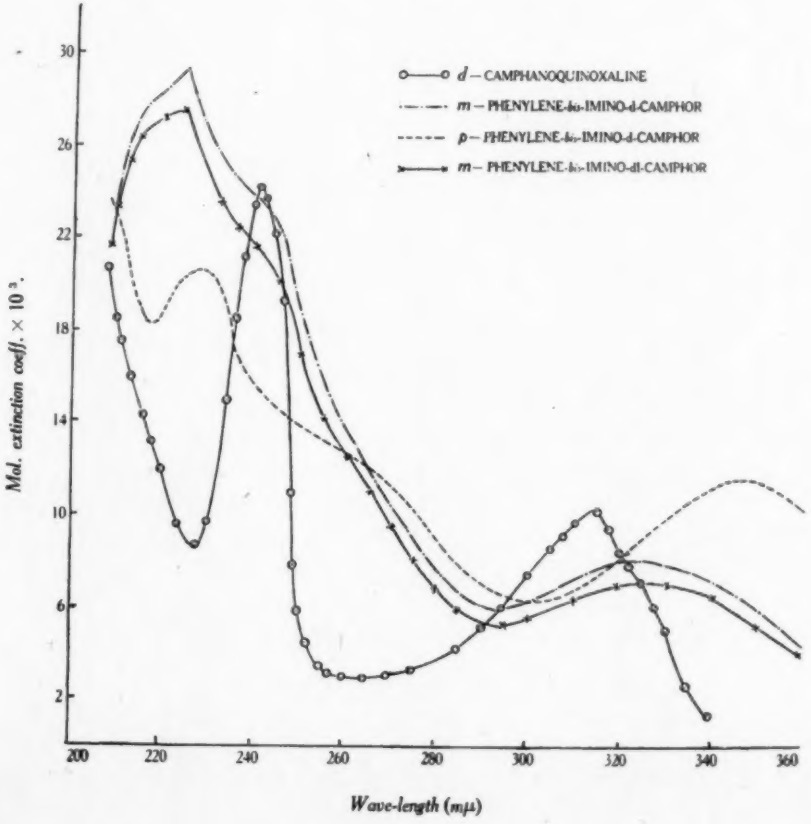
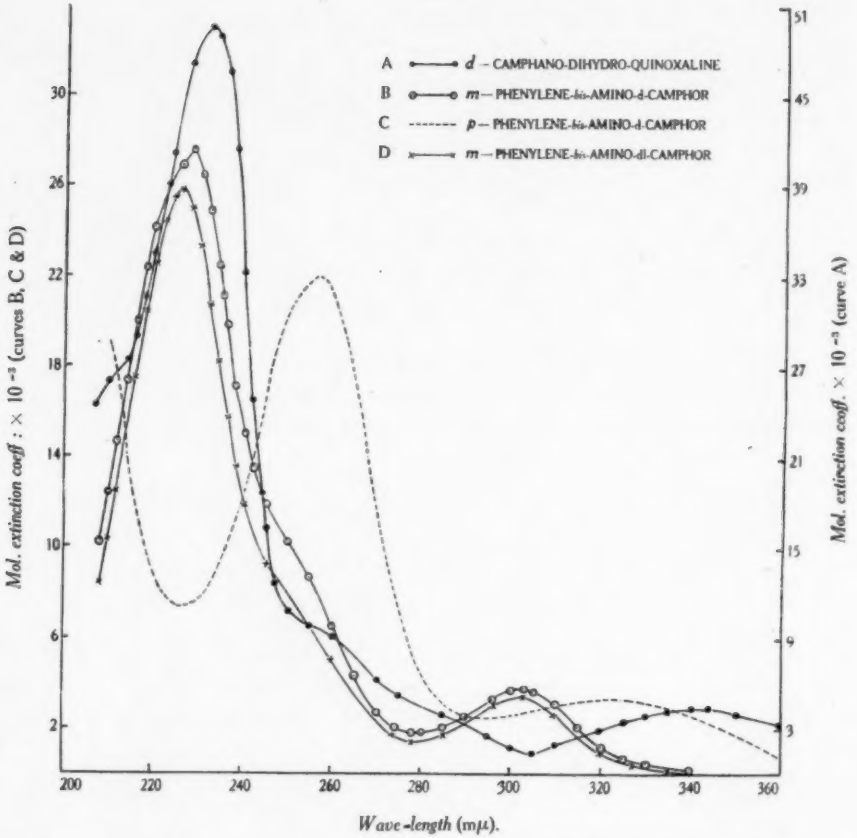


FIG. 2



corresponding amino derivatives, where the rotatory power of the *meta* isomer is higher than that of the *para* in all the solvents.

d-Camphanoquinoxaline shows relatively very low rotation (Tables I-II) which is due to the ring formation as in the case of *d*-camphoric acid, $[\alpha]^{35°}_{5461} = 56.°4$ and *d*-camphoric anhydride, $[\alpha]^{35°}_{5461} = 0°$ (Singh and Mahanti, *Proc. Ind. Acad. Sci.*, 1935, **2A**, 378). On reduction of *d*-camphanoquinoxaline to *d*-camphanodihydroquinoxaline, the rotatory power is further decreased so that the latter becomes *laevo*-rotatory.

It is noteworthy to observe that the rotatory power of *d*-camphanoquinoxaline is almost the same in all solvents excepting that it is slightly lower in chloroform.

Absorption Spectra of Dextro and Racemic Forms

By the application of Roozeboom's melting point—composition method, the racemic modifications of camphanodihydroquinoxaline and *p*-phenylene-*bis*-iminocamphor have been found (Singh and Saxena, *loc. cit.*) to be *solid solutions*, whereas those of camphanoquinoxaline, *m*-phenylene-*bis*-imino- and -aminocamphors are true *dl-compounds* in the solid state.

The absorption spectra of the *dextro* and *racemic* forms (Table III) are, however, similar and the curves superposable in all the cases as illustrated (Figs. 1 and 2) in the case of *m*-phenylene-*bis*-imino- and -aminocamphors. No existence of a true *dl-compound* is thus revealed by the study of absorption spectra. This is due to the *racemates* (*dl*) having dissociated completely into their optically active and opposite forms at such high dilutions.

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THE LIGHT SCATTERING BEHAVIOUR OF ALUMINIUM SUCCINATE GEL-FORMING SYSTEM

By U. M. Purao and D. M. Desai

The changes in depolarisation values and the intensity of transversely scattered light during the gelation process of aluminium succinate gel-forming mixtures have been studied. The results show that the particles increase in size during gelation and that they have spherical symmetry. The symmetry of the particles is not perceptibly disturbed in presence of acids and also by varying the concentration of gel-forming constituents. The intensity measurements reveal three distinct stages, viz., (i) a colloid is formed, (ii) hydration takes place, and (iii) the subsequent formation of a three-dimensional net-structure. The density and anisotropy scattering have been separated from the total intensity and their changes during the process of gelation are discussed. The dissymmetry: ratio $I_{45}°/I_{135}°$ fails to indicate the probable shape of the particles.

This investigation deals with the study of the depolarisation and intensity measurements of the transversely scattered light during the process of gelation of aluminium succinate gels. The object of this study is to examine closely the changes taking place in the size, shape and the aggregation of the colloidal particles during the sol-gel transformation and possibly to obtain an insight in the structure of these gels. The present study is in continuation of our previous work reported earlier on the light scattering behaviour of several inorganic gel-forming systems (cf. Jabalpurwala and Desai, this *Journal*, 1958, **35**, 645; *J. Univ. Bombay*, 1958, **27**, 20; 1957, **26**, 31).

Experimental

Aluminium succinate gels were formed by metathesis of aluminium chloride and sodium succinate solutions (cf. Mushran and Bose, *Curr. Sci.*, 1957, **26**, 47).

$AlCl_3.6H_2O$ (Merck's pure analytical quality, 50 g.) was dissolved in CO_2-free doubled distilled water. The strength of this solution in terms of aluminium oxinate was 102.34 g./litre. Sodium succinate (C.P.) was purified by recrystallisation, and a known weight of the recrystallised sample was dissolved to obtain a $3M/20$ solution. These two solutions were made dust-free by filtering them several times through sintered bed funnel (A.G. 201×4). A known volume of aluminium chloride solution (A) was taken in one test-tube and in another test-tube was taken the solution of sodium succinate (B), diluted with the requisite amount of distilled water so that the total volume of the gel-forming system was always 42.0 c.c. The two solutions were mixed and the resulting mixture was shaken for about 30 seconds. For the measurements of depolarisation and the intensity of scattered light, the gel-forming mixture was transferred to the optical cell and the measurements were made on the gel-forming system at certain known intervals of time. The depolarisation measurements were made by the well-known Cornu's method (cf. Prasad and Doss, *J. Coll. Sci.*, 1949, **4**, 349), taking all the necessary precautions, and the intensity of the scattered light was measured by the photomultiplier method, using the photomultiplier tube. The details of the circuit arrangement were described by Sundaram and Desai (*Proc. Nat. Inst. Sci.*, 1954, **20**, 598). The time of setting of gels was determined by Fleming's method (*Z. Physik*, 1902, **41**, 427).

The depolarisation values ρ_μ, ρ_v, ρ_h and the values of the intensity measurements $I_{90°}$ during the process of gelation in presence of varying concentrations of the constituents of the

gel-forming mixture and of acids are recorded in Tables I and II. The depolarisation values are expressed in percentages and the values of intensity are expressed in arbitrary units.

TABLE I

	A=15.0 c.c. B=22.8 c.c. Time of setting=195.0 mins.					A=13.8 c.c. B=22.8 c.c. Time of setting=130.0 mins.				
Time	ρ_μ.	ρ_v.	ρ_h.	$I_{90}°$.	$I_{45}°/I_{135}°$.	ρ_μ.	ρ_v.	ρ_h.	$I_{90}°$.	$I_{45}°/I_{135}°$.
1 min.	0.69	..	..	11.00	4.05	0.85	..	..	11.00	3.81
5	1.11	..	36.11	15.13	4.18	1.20	0.28	29.48	16.50	4.00
10	1.20	0.28	29.48	37.13	4.50	1.85	0.32	21.25	26.13	4.17
20	1.40	..	24.32	46.75	4.81	2.10	0.32	18.02	33.00	4.39
40	1.40	..	24.32	46.75	4.81	2.10	0.32	18.00	49.50	4.65
60	1.40	0.28	..	46.75	4.81	2.65	0.38	17.16	56.38	4.92
80	1.40	..	24.32	50.88	5.10	3.80	0.49	14.74	60.50	5.20
100	2.51	0.38	17.58	52.25	5.15	4.71	0.49	11.53	81.13	5.60
120	3.80	0.49	14.74	70.13	5.40	5.99	0.49	8.77	105.00	6.18
140	4.33	..	12.90	74.25	5.48	6.22	0.49	8.49	112.50	6.25
160	4.52	0.49	11.85	81.13	5.61	6.22	0.49	8.49	115.00	6.30
180	5.33	0.49	9.94	90.00	5.83	6.22	0.49	8.49	115.00	6.30
200	5.77	0.49	9.35	102.50	6.05	..	..	..	..	..
220	5.77	0.49	9.35	105.00	6.18	..	..	..	..	..
240	5.77	0.49	9.35	105.00	6.18	..	..	..	..	..

TABLE II

	A=15.0 c.c. B=24.0 c.c. Time of setting=155.0 mins. C=3.0 c.c. HCl (0.1 *N*)					A=15.0 c.c. B=24.0 c.c. Time of setting=160.0 mins. C=3.0 c.c. HNO_3 (0.1 *N*).				
Time	ρ_μ	ρ_v.	ρ_h.	$I_{90}°$.	$I^{45°}/I_{135}°$	ρ_μ.	ρ_v.	ρ_h.	$I_{90}°$.	$I_{45}°/I_{135}°$.
1 min.	0.62	..	..	11.00	3.87	0.62	..	..	11.00	3.87
5	0.69	0.19	..	16.50	4.00	0.69	1.19	38.29	16.50	4.00
10	1.11	..	..	34.38	4.21	1.01	..	29.48	30.25	4.23
20	1.20	0.28	29.48	39.88	4.53	1.01	0.23	29.48	38.50	4.48
40	1.30	..	27.10	39.38	4.53	1.01	0.23	..	38.50	4.48
60	1.40	0.28	24.32	45.38	4.67	1.40	..	24.32	44.00	4.85
80	1.40	0.28	24.32	46.75	4.75	1.40	0.28	24.32	49.50	5.15
100	1.97	0.32	19.82	56.38	5.27	1.85	0.32	21.25	60.50	5.45
120	3.43	0.49	15.52	64.63	5.59	3.43	0.49	15.52	74.25	5.70
140	4.52	0.49	12.19	82.50	5.93	4.92	0.49	11.20	82.50	5.90
160	5.54	0.49	9.65	97.50	6.14	5.54	0.49	9.65	97.50	6.14
180	5.54	0.49	9.65	100.00	6.19	5.54	0.49	9.65	100.00	6.23
200	5.54	0.49	9.65	100.00	6.19	5.54	0.49	9.65	100.00	6.23

From the tables both the initial and final values of ρ_v appear to show very little deviation from zero and that there is no appreciable change in the ρ_v values during the setting time. It can thus be inferred that the system contains particles which are spherical in shape. Further, it is seen that the variation in the concentration of the sodium succinate as well as aluminium chloride has no appreciable effect on the ρ_v values. Similar observations have been made when acids are added to these systems. It can thus be concluded that the symmetry of the particles in the gel-forming system under investigation is not perceptibly disturbed under these conditions. On the other hand, a general decrease in the values of ρ_h with the increase of time has been observed. These results indicate that the gelation is accompanied by increase in the size of the particles due to aggregation. The final values of ρ_h, which are about 10%, indicate that the size of the particles formed is fairly big as compared with the wave-length of the incident light used. Further, it has been observed that the values of ρ_h are higher in systems containing higher concentration of aluminium chloride. These systems therefore contain particles of comparatively small size. This is due to the peptising action of Al^{3+} ions. With increase in the concentration of sodium succinate, the values of ρ_h are found to decrease. This is attributed to the coagulating effect of this electrolyte. The addition of acids, on the other hand, results in imparting higher values of ρ_h to the system, which is due to the peptisation of larger aggregates in their presence.

The changes in the value of ρ_μ during the presence of gelation are due to the increase in values of ρ_v and decrease in the values of ρ_h, as ρ_μ depends on both these quantities (cf. Krishnan, *Proc. Ind. Acad. Sci.*, 1935, **1A**, 717, 782).

DISCUSSION

Intensity Measurements.—The changes in the intensity values of the transversely scattered light during the gelation are recorded in Tables I-II and are shown graphically in Figure 1. The intensity of the scattered light is observed to rise rapidly at first. It then remains steady for some time, and then there is again a rise in intensity, but this increase is comparatively small and more gradual than the initial rise. The intensity changes thus fall into three distinct steps, indicating that there are three distinct stages in the gel-formation. The following explanation seems plausible.

FIG. 1

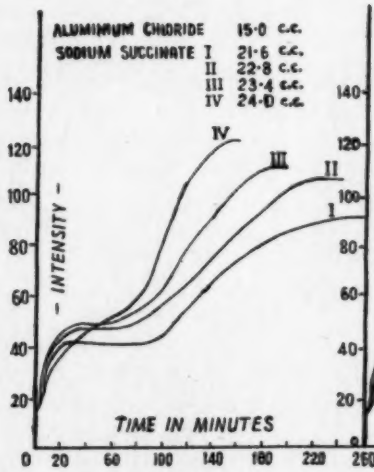
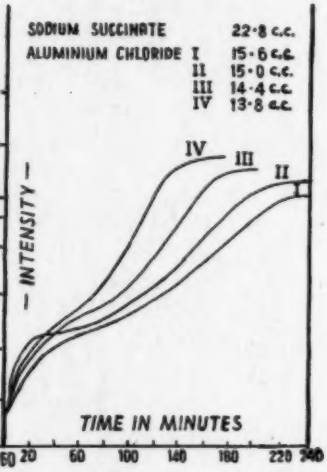


FIG. 2



In the initial stage, the scattering centres are being formed so that their number goes on increasing with time and, hence, the rapid increase in the intensity. The gel-forming substance formed as a result of the reaction between aluminium chloride and sodium succinate may be either aluminium succinate or a basic succinate of aluminium. It is possible that aluminium hydroxide may also be present in the gel-forming system formed as a result of hydrolysis of aluminium salt. Now ordinarily, hydration or solvation should proceed along with the formation of scattering centres, but the hydroxyl group present in the gel-forming system will delay the hydration of the particles. Viscosity measurements in the inititial stage showed that the hydration could not have been supposed to be functioning simultaneously with the formation of the gel-forming particles. The rapid increase in the intensity of the scattered light in the initial stage may thus be attributed to the formation of the colloidal particles in the system. At the end of the initial stage, the number of scattering centres formed reaches a maximum; thereafter, it appears that the particles undergo hydration and since water, bound or free, has the same refractive index, there is hardly any change in the intensity during this stage. The constant value of the intensity of the scattered light in the second stage may be thus attributed to the hydration of the gel-forming particles. At the end of the second stage, when the hydration is assumed to be complete, the aggregates of the colloid particles will begin to form due to which there will be a change in the size and shape of the

particles. Consequently, the intensity of the scattered light will begin to rise, and since this process is slow and gradual, the rise in the intensity will take place gradually and will not be as rapid as that in which the number of particles increases in the initial stage. The third stage of intensity changes during gelation represents this behaviour. The rise in the intensity of the scattered light during this stage is thus attributed to the formation of three-dimensional net-work in building of the gel structure.

Density and Anisotropy Scattering.—The density and the anisotropy scattering have been separated from the total intensity of the transversely scattered light. The total intensity, $I_{90°}$, is made up of density scattering, I_D, and anisotropy scattering, I_A. Zimm, Stein and Doty (*Polymer Bull.*, 1945, **1**, 90) have shown that the effect of anisotropy would be to increase the total intensity of scattering by a factor: $\rho = \frac{2\rho_v}{1+\rho_v}$.

Hence, the density scattering (I_D) would be given by

$$I_D = I \Big/ \left(\frac{6+6\rho}{6-7\rho}\right) \text{ i.e. } I_D = I \times \frac{6-7\rho}{6+6\rho}$$

and therefore the anisotropy scattering I_A would be be given by

$$I_A = I - I_D = I \times \frac{13\rho}{6+6\rho}.$$

The values of I_D and I_A, calculated by the above equations, are shown in Table III.

TABLE III

Aluminium chloride = 15.0 c.c. Sodium succinate = 24.0 c.c. Time of setting = 135.0 mins.

Time	ρ_v.	$\rho = \frac{2\rho_\mu}{1+\rho_v}$.	$\frac{6-7\rho}{6+6\rho}$.	$I_{90°}$.	I_D.	I_A.
10 mins.	0.28	0.0056	0.9977	34.38	34.30	0.08
20	0.28	0.0056	0.9977	45.38	45.28	0.10
40	0.32	0.0064	0.9862	46.75	46.12	0.63
60	0.38	0.0076	0.9833	50.50	49.12	0.84
80	0.43	0.0086	0.9815	57.75	56.69	1.06
100	0.49	0.0098	0.9790	82.50	80.69	1.81
120	0.49	0.0098	0.9790	100.00	97.90	2.10
140	0.49	0.0098	0.9790	120.00	117.50	2.50
160	0.49	0.0098	0.9790	120.00	117.50	2.50

It will be seen that the values of the density scattering, I_D, increase during the process of gel formation. Since the variation in I_D values is connected with the changes in the size of the particles, it can be inferred that the size of the particles increases gradually during the process of gelation. The values of anisotropy scattering, I_A, are found to be initially low, but as the gelation proceeds, the values of I_A show a little increase and become constant after the gel is set. The anisotropy scattering I_A would indicate the changes in the shape and/or structure of the particles. These observations would therefore show that in the initial stage, the particles appear to remain almost spherical and as the gelation proceeds, they tend to be anisotropic in shape and/or structure. The constant value of I_A after the gel is set would indicate that the anisotropic nature of the particles would not change after the process of gelation is complete.

A close examination of the changes in I_D and I_A values during the gelation would reveal that variation in the former values is more pronounced than in the latter. It can therefore be inferred

from these observations that the density scattering I_D predominates over the anisotropy scattering I_A throughout the process of gelation. This means that the increase in size of the particles is a predominant factor in the process of gelation, rather than increase in the anisotropy.

Dissymmetry: *Ratio* $I_{45}^{\circ}/I_{135}^{\circ}$.— The values of the ratio $I_{45}^{\circ}/I_{135}^{\circ}$ are recorded in the last column of Tables I and II. Since it has been inferred from the ρ_v values that the particles have almost spherical symmetry, it is expected that the dissymmetry should attain a very high value with the ultimate enormous growth of the scattering centres. The observed values of dissymmetry show a discrepancy from the values expected. In a gel-forming system, a three-dimensional net-work is formed and, as a consequence, the individual particle loses its independence. Consequently, there is a possibility of considerable multiple scattering and absorption which will affect the value of dissymmetry. The observed discrepancy in the value of this ratio appears to be due to multiple scattering and absorption in this system.

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*ISO*QUINOLINE DERIVATIVES AS POSSIBLE AMOEBACIDES. PART II

BY T. N. GHOSH, SUNIL KUMAR GANGULY AND R. N. BHATTACHARYA

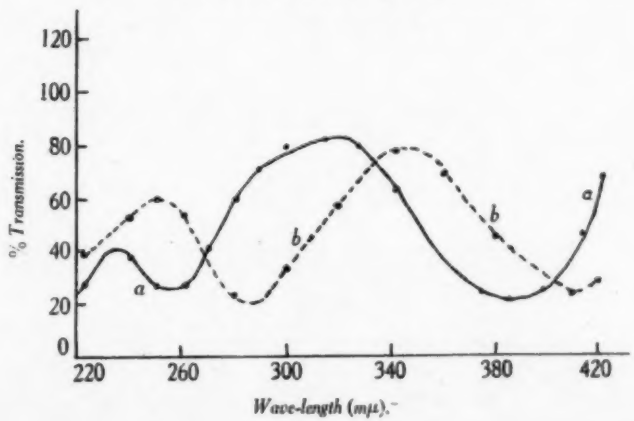
The Bischler-Napieralski cyclisation of malondi-β-phenethylamide with P_2O_5 has led to the formation of a mixture of (I) and (II). The constitutions of (I), its dehydrogenated product (III) and of (II) have been discussed in the light of their ultraviolet absorption spectra.

It has been recorded in Part I (this *Journal*, 1959, **36**, 699) that malondi-β-phenethylamide undergoes the Bischler-Napieralski cyclisation in presence of P_2O_5 to yield 1:1′-methylene-*bis*-3:4-dihydro*iso*quinoline (I). Repetition of the reaction with a larger quantity of the amide has now led to the isolation, besides (I), of another basic compound in poor yield, which, on elemental analyses, appears to be 1-(*N*-β-phenethylacetamido)-3:4-dihydro*iso*quinoline (II). The constitution of (II) has been established by conversion, with P_2O_5, into (I).

The striking feature of the compound (I) is its fine yellow colour, which is further deepened by hydrogen chloride absorption in ethanolic solution. It has been recorded (Part I, *loc. cit.*) that dehydrogenation of (I) over Pd—C leads to the formation of the fully aromatised *iso*quinoline (III) as a cream-coloured solid, but the colour is now found to remain unaffected by hydrogen chloride absorption in ethanolic solution. These observations tend to suggest the presence of conjugation in the compound (I). In order to establish this point, the absorption spectra of (I), its dehydrogenated product (III) and of (II) have been studied. It is found that, whereas the absorption spectrum of (III) (Fig. B) and that of (II) (Fig. C) resemble those of normal *iso*quinoline derivatives, e.g., 1-methyl-3:4-dihydro*iso*quinoline and 1-benzyl-3:4-dihydro*iso*quinoline (cf. Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 957), the absorption spectra (Fig. A) of (I) in ethanolic solution and in normal ethanolic hydrogen chloride solution present quite a different picture. The latter indicate the presence of conjugation in (I), both in ethanolic as well as in

FIG. A

U. V. spectrum of (I) (0.001072% *solution*).



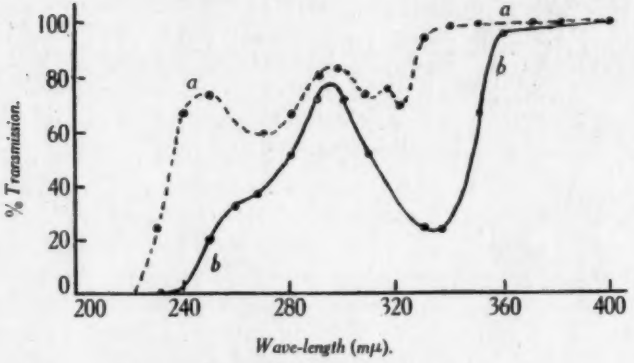
a. in ethanol : ●—●—●

b. in ethanolic HCl (*N*) : ●.....●

ethanolic hydrogen chloride solutions, brought about by a double bond, exocylic to the *iso*quinoline ring. But as the intensity of absorption is greater, in the present case, in ethanolic hydrogen chloride solution than in ethanolic solution, it is considered that the base (I) in ethanolic hydrogen chloride may exist in the form (IV) and the same in ethanolic solution exists as an equilibrium mixture of (I) and (IV).

FIG. B

U. V. spectrum of (III) (0.00134% *solution*).

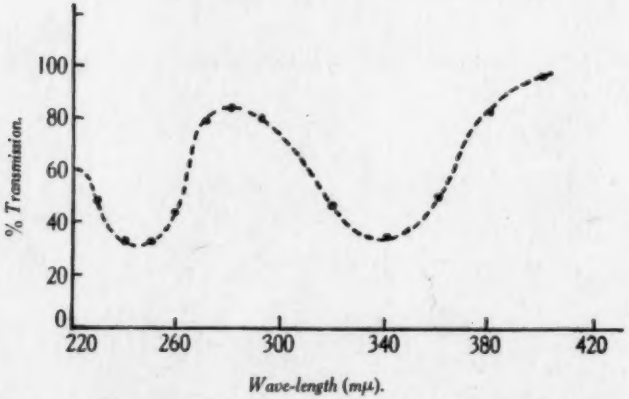


a. in ethanol : ●—●—●

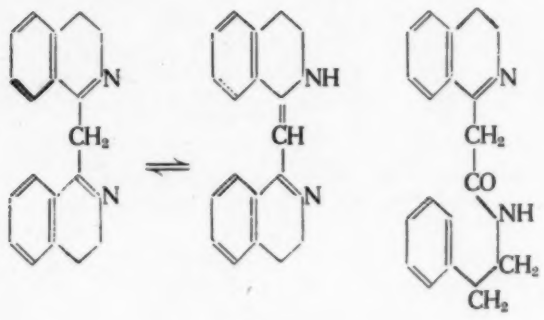
b. in ethanolic HCl (*N*) : ●.....●

FIG. C

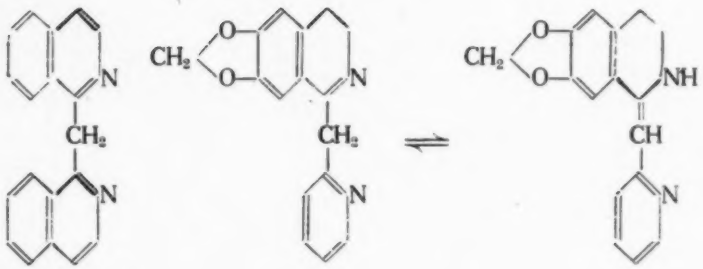
U. V. spectrum of (II) *in ethanol* (0.000939% *solution*).



In the literature 1-(α-picolyl)-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (V) (Clemo *et al.*, *J. Chem. Soc.*, 1936, 610), which is structurally related to (I), is being found to show characteristics comparable to those of (I). On the basis of ultraviolet absorption spectrum, Bills and Noller (*loc. cit.*) have adduced evidence to show that the yellow colour of this α-picoly*liso*quinoline derivative is due to conjugation between the two aromatic rings. In other words, the base (V) exists in the form: 1-(α-picolal)- 1:2:3:4-tetrahydro-6:7-methylenedioxy*iso*quinoline (VI).



(I) (IV) (II)



(III) (V) (VI)

EXPERIMENTAL

Action of P_2O_5 *on Malondi-β-phenethylamide : Formation of* 1:1′-*Methylene*-bis-3:4-*dihydroisoquinoline* (I) *and* 1-(N-β-*phenethylacetamido*)-3:4-*dihydroisoquinoline* (II).—A mixture of malondi-β-phenethylamide (32 g.) and P_2O_5 (128 g.) in anhydrous toluene (640 c.c.) was refluxed under mechanical stirring in an oil-bath for 4 hours. The mixture was cooled in ice and treated with ice-water. The aqueous layer was separated, washed with ether and filtered. The filtrate, on basification with NaOH, furnished a pasty solid which was purified by acid-alkali treatment. The pasty solid (11.3 g.), dried *in vacuo* over H_2SO_4 (conc.), was triturated with warm benzene and the insoluble portion* was filtered.

The filtrate was evaporated on the steam-bath, when a dark pasty mass was obtained. On trituraion with ethanol, a fine yellow solid (3.4 g.) was obtained, which, on crystallisation with ethanol, was found to be (I) (cf. Part I, *loc. cit.*).

The solid* (II, 1.6 g.) was crystallised from aqueous ethanol in colorless needles, m.p. 160-61°. It was dried *in vacuo* over P_2O_5 at 100°. (Found: C, 78.34; H, 6.72; N, 9.18. $C_{19}H_{20}ON_2$ requires C, 78.08; H, 6.85; N, 9.59%). It is readily soluble in cold dilute hydrochloric acid and precipitated by alkali. When treated with P_2O_5 under conditions as employed above, it was converted into (I).

Absorption Spectra.—For the determination of absorption spectra, the compounds were dissolved in ethanol suitable for UV studies. The dilution was made with an "Agla" brand Micrometer Syringe (B & W) using ethanol or ethanolic hydrogen chloride as the case may be. The readings were taken in a Beckman model DU spectrophotometer provided with 1 cm silica cells.

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BERYLLIUM FLUORIDES. PART II. FORMATION OF BERYLLIUM FLUORIDES IN SOLUTION

By Apurba Kumar Sengupta*

Beryllium is known to be capable of combining with one or more fluoride ions to furnish several simple and complex fluorides. From conductometric titrations of the systems: Be $(NO_3)_2$–KF, BeF_2–KF, BeF_2–HF, and thermometric titration of HF by BeF_2, the existence of BeF^+ ion, BeF_2(slightly dissociated), BeF_4^{2-} ion, and of H_2BeF_4 acid has been confirmed, but the existence of BeF_3^-, BeF_5^{3-} or BeF_6^{4-} ions, and of $HBeF_3$ acid could not be corroborated.

A search in literature shows that beryllium combines with one or more fluoride ions to furnish several simple and double fluorides :

$$Be^{2+} + nF^- = BeF_n^{(n-2)-}, \text{ (where } n = 1,2,3,4, \text{ etc.)}.$$

The existence in solution of BeF^+ ion, $HBeF_3$ and H_2BeF_4 acids was reported by Tananaev and Deichman (*Bull. Acad. Sci., U.R.S.S., Classe Sci. chim.*, 1947, 591 ; *Izvest Akad. Nauk, S.S.S.R., Otdel Khim. Nauk*, 1949, 144 ; *ibid.*, 1951, 26). Purkayastha (this *Journal*, 1947, **24**, 257) reported the existence in solution of BeF_2, BeF_3^-, BeF_4^{2-}, BeF_5^{3-} and BeF_6^{4-} ions. The trifluoberyllates have been shown to be trimeric in the solid state (O'Daniel and Tscheischwili, *Naturwiss.*, 1943, **31**, 209; *Jahrb. Min., Geol. Monatsh.*, 1945, **48A**, 56), and are known to be non-recrystallisable from water (Simons, "Fluorine Chemistry", II, 1954, p 4, Academic Press Inc., N.Y.). These facts, thus, necessitate further investigation of the formation of trifluoberyllate ion, and determination of its degree of condensation in solution. The report of the existence of BeF_5^{3-} and BeF_6^{4-} ions requires further confirmation since the radius ratio of beryllium and fluoride ions demands tetra-co-ordination for beryllium.

The present author has investigated the formation of beryllium fluorides in solution by conductometric and thermometric titrations (Grobet and Dutoit, *J. chim. phys.*, 1921, **19**, 324) and by Job's method of continued variation (*Ann. chim.*, 1928, *x*, **9**, 113) taking conductivity as the index property.

Experimental

Beryllium nitrate (Schering and Kahlbaum's) was dissolved in water. The solution on estimating for beryllium and nitrate showed the presence of basic beryllium salt, and therefore during the titrations calculated amounts of distilled nitric acid were added to prepare normal salt solutions. The ammonium and potassium tetrafluoberyllates, $(NH_4)_2BeF_4$ and K_2BeF_4, were prepared in the usual way and recrystallised from water. Beryllium fluoride was prepared from ammonium tetrafluoberyllate according to Lebeau's method (*Compt. rend.*, 1898, **126**, 1418). Potassium and sodium fluorides were prepared from E. Merck's reagent grade carbonate and hydrofluoric acid, and heating the products with a Meker burner for several hours. Other reagents used were of reagent grade.

The conductance of the solutions was measured with a Kohlrausch Universal Bridge, Cat. No. 7401, W. G. Pye and Co. Ltd., Cambridge, England. The conductometric titrations (Figs. 1, 2, 3 and 4) were performed in a plastic vessel. The stirring was done with a polyethylene-enclosed

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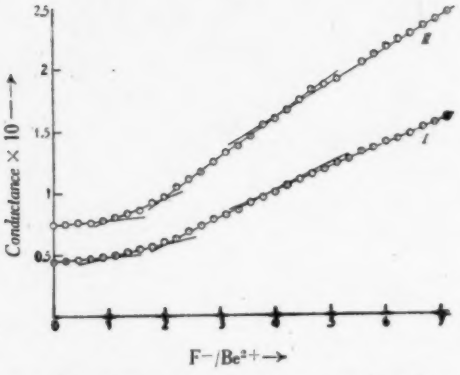
magnetic stirrer. The glass stems of the two platinised electrodes were carefully covered with wax prior to platinising the electrodes. Fig. 1 depicts the results of titration of beryllium nitrate by potassium fluoride. In Fig. 2 the differences of the conductances observed in the titration of KF

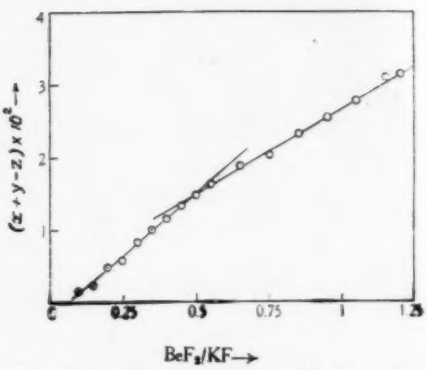
FIG. 1



1. Curve I. 50 c.c. of beryllium nitrate solution (0.0179 *M* Be) [prepared by mixing 10 c.c. beryllium nitrate solution (0.08956 *M* with respect to Be and 0.1692 *M* with respect to nitrate), 0.4 c.c. HNO_3 (0.246 *N*) and 39.6 c.c. water] titrated by potassium fluoride (0.993 *M*).

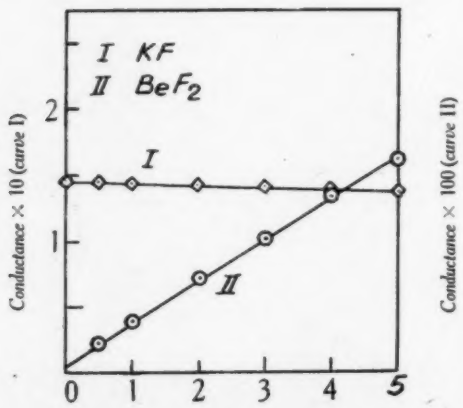
Curve II. 58.8 c.c. of beryllium nitrate solution (0.03046 *M* Be) prepared in the above manner titrated by potassium fluoride (0.993 *M*).

FIG. 2



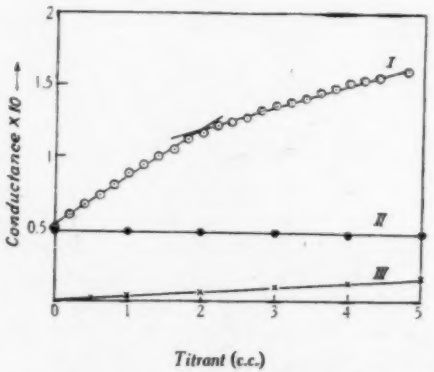
2. The differences of the conductances observed in the titration of 70 c.c. of KF (0.1042 *M*) by BeF_2 (1.827 *M*), and the sum of the conductances in the blank titrations as shown in Fig. 3, against mole ratio BeF_2/KF.

FIG. 3



3. Curve I. 70 c.c. of KF (0.1042 *M*) titrated by water.
Curve II. 70 c.c. water titrated by BeF_2 (1.827 *M*).

FIG. 4



4. Curve I. 70 c.c. hydrofluoric acid (0.1027 *M*) titrated by beryllium fluoride (1.827 *M*).

Curve II. 70 c.c. of hydrofluoric acid (0.1027 *M*) titrated by water.

Curve III. 70 c.c. of water titrated by beryllium fluoride (1.827 *M*).

by BeF_2, and the sum of the conductances observed in the corresponding blank titrations (Fig. 3), were plotted against the mole ratio BeF_2/KF. In Fig. 4 the results of conductometric titration of hydrofluoric acid by beryllium fluoride have been shown along with the corresponding blank titrations. Conductometric titrations according to Job's method of continued variation of the systems BeF_2 — KF (0.04*M*), K_2BeF_4 — BeF_2 (0.02*M*), K_2BeF_4 — NaF (0.04*M*), and $(NH_4)_2BeF_4$—KF (0.08 *M*) were performed with equimolar solutions as usual, the solutions being kept in wax-coated tubes having rubber stoppers. The data of these titrations have, however, not been submitted (vide Discussion).

The thermometric titration of hydrofluoric acid by beryllium fluoride (Fig. 5) was performed with the usual precautions, hydrofluoric acid being taken in a plastic vessel which was in turn placed inside the Dewar flask contained in a thermally insulated box. The Beckmann thermometer was thinly coated with wax in such a way that there was no difficulty in measuring the change in temperature of the solution. The temperature change at a constant volume has been plotted against the volume of beryllium fluoride added.

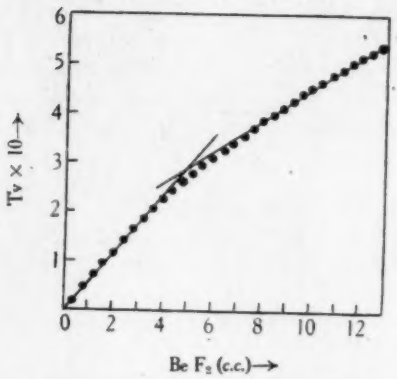
DISCUSSION

The conductometric titration of beryllium nitrate by KF (Fig. 1) shows breaks in the curves at the Be : F ratios of 1 : 1, 1 : 2 and 1 : 4. These inflection points therefore correspond to the formation of BeF^+ ion, BeF_2 (slightly dissociated) and BeF_4^{2-} ions. The break corresponding to BeF_4^{2-} ion, however, is not a sharp one. The formation of BeF_4^{2-} ion has been confirmed by the conductometric titration of KF by BeF_2 (Fig. 2). These titration curves show the absence of BeF_2^-, BeF_5^{3-} and BeF_6^{4-} ions. The conductometric titration curve (Fig. 4) obtained by titrating hydrofluoric acid by beryllium fluoride shows only one break corresponding to tetrafluoberyllic acid, H_2BeF_4. The blank titration, viz., hydrofluoric acid by water, shows that H_2BeF_4 is a stronger acid than hydrofluoric acid.

The study of the systems : K_2BeF_4 — BeF_2, BeF_2 — KF, K_2BeF_4 — NaF and $(NH_4)_2BeF_4$ — KF, according to Job's method of continued variation taking conductivity as the index property, showed that in all these systems the conductance of the mixtures was always less than the sum of the conductances recorded with the corresponding blank mixtures, and the magnitude of the difference was found to be very small, becoming slightly higher at approximately 1 : 1 molar ratio of the reactants. The differential curves of the recorded conductances plotted against volume of any reactant showed erratic results. Hence, the reasons for not submitting these data are apparent. The fall in conductance of the mixtures from the sum of the blanks in the system K_2BeF_4 — BeF_2, however, showed the absence of BeF_3^- ion, the formation of which could be anticipitated to result in an increase in conductance, assuming the mobility of BeF_3^- ion to be not less than that of BeF_4^{2-} ion. These results suggest that conductance being strictly not a linear property, its use in Job's method of continued variation should better be avoided (cf. Jones and Innes, *J. Phys. Chem.*, 1958, **62**, 1005).

The thermometric titration curve (Fig. 5) obtained by titrating hydrofluoric acid by beryllium fluoride showed only one break corresponding to the formation of tetrafluoberyllic acid, H_2BeF_4, and no indication of any other fluoberyllic acids could be found. Thus, the result of corresponding conductometric titration was corroborated by a different method.

FIG. 5



60 c.c. of hydrofluoric acid (0.3103 *N*) titrated thermometrically by beryllium fluoride (1.827 *M*).

Author's grateful thanks are due to Prof. P. B. Sarkar, Head of the Department of Pure Chemistry, for encouragement, suggestions, and providing all laboratory facilities. Author is also deeply indebted to Sri N. N. Ghosh for his suggestions.

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HYDROXYKETONES. PART X. HYDROXYKETONES AND THEIR REDUCTION PRODUCTS AS EFFECTIVE LARVICIDES

By S. C. Aggarwal and G. S. Saharia

Esters of phenol, isomeric cresols and naphthols with *m*-chlorobenzoic acid have been subjected to the Fries migration and the resulting hydroxyketones reduced to give rise to substituted diphenylmethanes as possible larvicides. Some of these and others, prepared by reduction of the hydroxyketones obtained from the phenolic esters of *o*-chlorobenzoic acid, have been tested and found to be effective against D.D.T.-resistant and susceptible *C. fatigans*.

The present work, which is a continuation of our earlier studies on the mechanism of the Fries migration (Saharia, *J. Sci. Ind. Res.*, 1954, **13B**, 544; Saharia *et al.*, this *Journal*, 1958, **35**, 133 et seq; *J. Vk. Univ.*, 1958, **2**, 143), deals with the migration of the phenyl, isomeric cresylic and naphthyl esters of *m*-chlorobenzoic acid and subsequent reduction of some of the hydroxyketones.

Phenols as bactericides are known from early times (cf. Suter, *Chem. Rev.*, 1941, **28**, 269). The halogen atoms and the alkyl groups, when attached to the aromatic nucleus, enhance greatly the bactericidal activity, the positions of these hardly having any appreciable effect. Klarmann *et al.* (*J. Amer. Chem. Soc.*, 1932, **44**, 3323; U.S. Pat., 1934, 1,967,825) have investigated the properties of some chloro derivatives of hydroxydiphenylmethane and reported these to be highly potent as bactericides; here again, the positions of the substituents do not greatly matter, though the activity enhances with the size of the alkyl group.

These hydroxydiphenylmethanes were prepared by direct condensation of the appropriate phenol with chlorobenzoyl chloride in presence of anhydrous aluminium chloride. Preparation of such compounds is not very convenient and it is often difficult to obtain the chlorobenzoyl chlorides. In contrast to this, the method reported herein is simpler and consists in condensing phenols with *m*-chlorobenzoyl chloride to yield the corresponding esters. These esters on the subsequent Fries transformation at 120° and 160° furnished the *ortho*- and *para*-hydroxyketones which were separated by solubility difference in aqueous sodium carbonate. Reduction of some of the hydroxyketones to the corresponding diphenylmethanes was carried out by Clemmensen's method (Table II). Some of these and others, obtained by reduction of the hydroxyketones isolated on migrating the phenyl esters of *o*-chlorobenzoic acid, were tested as adulticides against house flies (*M. nebulo*) and as larvicides against mosquitoes (*C. fatigans*), comparative tests being carried out with D.D.T. under identical conditions. As larvicides these were found to be toxic to *C. fatigans* larvæ, though in their effectiveness these did not compare favourably with D.D.T.; the most toxic of these was 4-hydroxy-3′-chlorodiphenylmethane. These compounds were also tested for their toxicity against D.D.T.-resistant *C. fatigans* larvæ and were found to be effective against them, 4-hydroxy-3′-chlorodiphenylmethane having been found the most effective against D.D.T.-resistant larvæ (Table III).

Experimental

Preparation of Esters.—An equimolar mixture of *m*-chlorobenzoyl chloride and phenol was refluxed until the evolution of hydrogen chloride had ceased; water was added to the cooled product and the separated ester was extracted with ether. The ethereal solution after washing with 2% aqueous

NaOH and water was dried and the ether recovered. The residue was crystallised from ethanol. Analytical data, m.p., crystalline shape and yields of the phenol esters of *m*-chlorobenzoate are recorded in Table I.

TABLE I

	Phenol esters.	Cryst. shape.	M.P.	%Yield.	Formula.	% Carbon. Found.	Calc.	% Hydorgen. Found.	Calc.
I.	Phenyl	Colorless plates	59°	98.4		..		..	
II.	*p*-Cresyl	Colorless long needles	79°	85.0	$C_{14}H_{11}O_2Cl$	68.7	68.1	4.7	4.4
III.	*m*-Cresyl	Colorless leaflets	50-51°	77.6	,,	68.4	68.1	4.7	4.4
IV.	*o*-Cresyl	..	54°	73.2	,,	68.2	68.1	4.4	4.4
V.	α-Naphthyl	Colorless tiny needles	73°	91.8	$C_{17}H_{11}O_2Cl$	72.5	72.2	3.7	3.8
VI.	β-Naphthyl	Colorless plates	97°	94.6	,,	72.0	72.2	4.0	3.8

The *Fries migration of the esters* was carried out, using 1.3 moles of anhydrous aluminium chloride and one mole of the ester, in absence of any solvent, at 120° and 160° and the reaction products were worked up in the customary manner.

Hydroxyketones

Phenyl *m*-chlorobenzoate (I) furnished the following two ketones.

(*a*). 4-*Hydroxy-3'-chlorobenzophenone* was crystallised from ethanol in colorless needles, m.p. 172°. (Found : C, 66.9 ; H, 3.8. $C_{13}H_9O_2Cl$ requires C, 67.1 ; H, 3.8%). It did not show any characteristic coloration with ferric chloride. It formed a 2 :4-dinitrophenylhydrazone, m.p. 220°.

(*b*). 2-*Hydroxy-3'-chlorobenzophenone* was crystallised from ethanol in pale yellow plates, m.p. 89°. (Found : C, 67.4 ; H, 3.8. $C_{13}H_9O_2Cl$ requires C, 67.1 ; H, 3.8%). It developed a deep reddish brown colour with ferric chloride. Its 2 :4-dinitrophenylhydrazone melted at 228°.

The ester (II) afforded only 2-*hydroxy-5-methyl-3'-chlorobenzophenone* as yellow hexagonal plates from petroleum ether, m.p. 72°. (Found : C, 68.1 ; H, 4.7. $C_{14}H_{11}O_2Cl$ requires C,68.1 ; H, 4.4%). It developed a deep violet colour with $FeCl_3$. Its 2 : 4-dinitrophenylhydrazone melted at 223°.

The ester (III) yielded the following two ketones, which were fractionally separated by their solubility difference in petroleum ether.

(*a*). 2-*Hydroxy-4-methyl-3'-chlorobenzophenone* was crystallised in fine needles from ethanol, m.p. 89°. (Found : C, 68.8 ; H, 4.7. $C_{14}H_{11}O_2Cl$ requires C, 68.1 ; H, 4.4%). It showed a deep reddish brown colour with $FeCl_3$. Its 2 :4-dinitrophenylhydrazone melted at 229°.

(*b*). 2-*Methyl-4-hydroxy-3'-chlorobenzophenone*, m.p. 108°. (Found : C, 68.7 ; H, 4.7. $C_{14}H_{11}O_2Cl$ requires C, 68.1 ; H, 4.4%). It did not show any coloration with ferric chloride. Its 2 :4-dinitrophenyl-hydrazone had m.p. 238-39°.

The ester (IV) furnished only 3-*methyl-4-hydroxy-3'-chlorobenzophenone* as colorless plates from acetone-alcohol mixture, m.p. 149-50°. (Found : C, 67.8 ; H, 4.2. $C_{14}H_{11}O_2Cl$ requires C, 68.1 ; H, 4.4%). It did not show any $FeCl_3$ colour reaction in aqueous medium. Its 2 :4-dinitrophenylhydrazone melted at 237-38°.

The ester (V) yielded only *3'-chlorophenyl-1-hydroxynaphthyl-4-ketone* as bright red tiny crystals from benzene-petroleum ether, m.p. 178°. (Found : C, 72.8 ; H, 3.9. $C_{17}H_{11}O_2Cl$ requires C, 72.2 ; H, 3.8%). Its 2 :4-dinitrophenylhydrazone had m.p. 181-82° and gave no $FeCl_3$ colour reaction.

The ester (VI) afforded *3'-chlorophenyl-2-naphthyl-1-ketone* as yellow needles from benzene, m.p. 104-105°. (Found : C, 71.9 ; H, 4.0. $C_{17}H_{11}O_2Cl$ requires C, 72.2 ; H, 3.8%). It developed a deep reddish brown colour with $FeCl_3$. It did not form any 2 :4-dinitrophenylhydrazone.

Chlorodiphenylmethanes

Amalgamated zinc (6 g.) contained in a r.b. flask (100 c.c.) was covered with water (1 c.c.) and HCl (conc., 12 c.c.) ; hydroxyketone (3 g.) was then added and the content refluxed for 24 hours. On cooling, the reaction product was extracted with ether, the ethereal solution was washed and dried and after the recovery of the solvent, the reduced product was purified by distillation. Results are recorded in Table II.

TABLE II

Ketone.	Reduced product.	B.P.	3:5-Dinitrobenzoate m.p.
4-Hydroxy-3'-CB	4-Hydroxy-3'-CDM	184° 10 mm	151°
2-Hydroxy-3'-CB	2-Hydroxy-3'-CDM	182°/9	103-104°
2-Hydroxy-5-methyl-3'-CB	2-Hydroxy-5-methyl-3'-CDM	120°/9	154°
2-Hydroxy-4-methyl-3'-CB	2-Hydroxy-4-methyl-3'-CDM	186-87°/9	108-109°
3-Methyl-4-hydroxy-3'-CB	3-Methyl-4-hydroxy-3'-CDM	100°/11	134°

Larvicidal tests of several derivatives of the chlorodiphenylmethane are recorded in Table III.

TABLE III

Against D.D.T. resistant *C. fatigans*.				Against susceptible *C. fatigans*.		
M.L.C. (p.p.m.)	% Mortality.	Conc. (p.p.m.)	Compounds.	Conc. (p.p.m.)	% Mortality.	M.L.C. (p.p.m.)
	95.8	10.0	2-Hydroxy-5-methyl-3'-CDM	10.0	98.3	
4.5	57.3	5.0		5.0	54.5	4.3
	5.5	2.0		2.0	9.0	
	98.0	10.0	3-Methyl-4-hydroxy-3'-CDM	10.0	100.0	
	98.3	20.0	2-Hydroxy-3'-CDM	20.0	100.0	
10.7	78.4	15.0		10.0	85.0	3.9
	35.2	10.0		2.5	31.4	
	5.2	5.0		1.25	11.0	
	100.0	10.0	4-Hydroxy-3'-CDM	10.0	100.0	
3.4	96.8	5.0		5.0	99.1	1.7
	63.3	2.5		1.25	33.0	
	41.6	1.25	2-Methyl-4-hydroxy-3'-CDM	20.0	10.0	
	91.2	20.0		15.0	79.6	12.6
	72.5	15.0		10.0	20.2	
	6.2	10.0		5.0	2.5	
	75.9	20.0	4-Hydroxy-2'-CDM	20.0	100.0	
15.6	24.1	15.0		15.0	86.6	9.02
	10.8	10.0		10.0	58.1	
	0.9	5.0				
	100.0	20.0	3-Methyl-4-hydroxy-2'-CDM	20.0	100.0	
	95.3	20.0		20.0	99.2	

TABLE III (*cont'd.*)

Against D.D.T. resistant *C. fatigans.*				Against susceptible *C. fatigans.*		
M.L.C. (p.p.m.)	%Mortality.	Conc. (p.p.m.)	Compounds.	Conc. (p.p.m.)	% Mortality.	M.L.C. (p.p.m.)
	92.6	15.0	2-Hydroxy-5-methyl-2'-CDM	20.0	99.2	
10.3	38.2	10.0		15.0	79.8	9.8
	5.3	5.0		10.0	41.7	
	100.0	20.0	2-Hydroxy-4-methyl-2'-CDM	5.0	19.2	
12.6	95.8	15.0		20.0	99.6	
	66.2	10.0		15.0	83.3	8.9
	6.4	5.0		10.0	67.8	
	63.0	20.0	*bis*-(*p*-Chlorophenyl)- trichloroethane (D.D.T.pp.)	5.0	14.2	
				2.5	91.0	
15.0	34.0	10.0		0.5	71.0	0.23
	12.0	2.5		0.1	28.7	

N. B, CB=Chlorobenzophenone, CDM=Chlorodiphenylmethane.

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COMPLEX COMPOUNDS OF ALUMINIUM WITH MANDELIC ACID

By S. N. Srivastava and Manohar

From pH and conductance measurements it is concluded that mandelic acid is a good chelating agent for aluminium. Three chelates corresponding to 1:1, 1:2 and 1:3 formulae are formed. The chelate of composition 1:1 is formed at a lower pH value, while 1:2 and 1:3 chelates, which occur at pH 6.5 and 7.8 respectively, are more stable than 1:1 chelate. The chelation takes place easily on account of the close proximity of the acidic and electron-donating groups, a fact which is essential for formation of the ring containing the metal atom.

There are many references in literature of complexes of aluminium with aliphatic as well as aromatic hydroxy-acids. Aluminium chelates with salicylic acid were first studied by Burrows and Wark (*J. Chem. Soc.*, 1928, 455). A detailed study of these complexes was carried out by Babko *et al.* (*J. Gen. Chem., U.S.S.R.*, 1948, **18**, 1617). But studies on complexes of aluminium with mandelic acid are lacking. This work concerns the present study.

Experimental

First a solution of aluminium chloride (A.R., B.D.H.) of approximate strength was prepared. Its aluminium content was estimated gravimetrically by precipitating aluminium as aluminium oxinate (Vogel, "Text-Book of Quantitative Inorganic Analysis", 1951, p. 372). Mandelic acid used was of A.R. quality of B.D.H.

pH of the solution was determined by a Beckman pH meter, H_2 type, having a glass and a saturated calomel electrodes. The instrument was standardised with a standard buffer solution supplied by the manufacturers. Electrical conductivity was measured by Gallen Kamp's Kohlrausch slide wire with an audio-frequency oscillator in the circuit, the null point being detected by means of a headphone.

In all the measurements monovariant method was adopted. To constant volumes of aluminium chloride varying amounts of chelating agent were added. Thus three sets of mixtures containing aluminium chloride and chelating agent in the ratio of 1 : 1, 1 : 2 and 1 : 3 were prepared. To these mixtures varying quantities of NaOH solution of known strength were added. The total volume in every case was kept constant. The solutions were left for about 24 hours to attain equilibrium. pH and specific conductance of the mixtures were determined at a constant temperature of 20.5°. For comparison, aluminium chloride and mandelic acid were titrated potentiometrically and conducotimetrically with a standard alkali solution under the same conditions.

Only the representative pH data for 1 : 1 mixture are shown in Table I, while others have been depicted in graphs (Figs. 1 and 2).

Table I

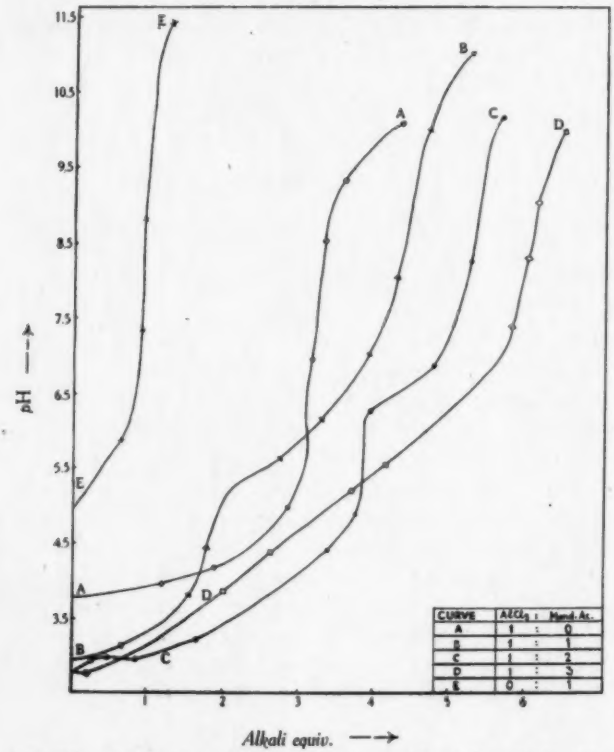
pH values of 1:1 *mixture of aluminium chloride and mandelic acid at different concentrations containing different quantities of alkali.*

Equiv. alkali added.	pH values at *M*/250.	*M*/500.	*M*/1000.	Equiv. alkali added.	pH values at *M*/250.	*M*/500.	*M*/1000.
0.0	3.00	3.05	3.10	2.8	5.70	5.90	6.00
0.2	3.05	3.10	3.15	3.0	5.80	6.10	6.20
0.4	3.10	3.17	3.20	3.4	6.20	6.50	6.80
0.8	3.30	3.37	3.40	3.8	6.70	7.10	7.30
1.2	3.55	3.60	3.70	4.2	7.70	8.20	8.30
1.6	3.87	3.98	4.35	4.6	9.30	10.80	10.90
2.0	5.15	5.30	5.50	5.0	10.60	11.40	11.45
2.4	5.40	5.55	5.70	5.4	11.00	11.50	11.55

DISCUSSION

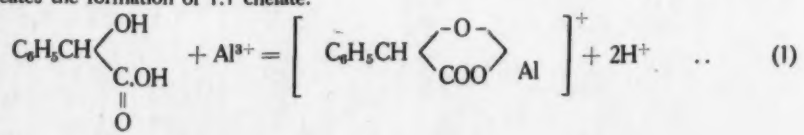
Fig. 1 represents the changes in the *p*H occurring when aluminium chloride, mandelic acid and their mixtures are titrated with alkali. Curve A (1:0) is for *M*/250 aluminium chloride solution alone; while curves B to D are for 1:1 to 1:3 mixutres. Curve E represents *p*H changes when only mandelic acid (*M*/250) is titrated against alkali.

FIG. 1



From curve A (Fig. 1) it is clear that precipitation of aluminium hydroxide starts at *p*H 5.2, when nearly three equivalents of alkali have been added. At *p*H 9.8, when nearly four equivalents of alkali have been added, the above precipitate dissolves to furnish sodium aluminate.

Curve E shows at once that there is a sudden rise in *p*H, when nearly one equivalent of alkali has been added. In case of curve B, which represents *p*H changes for 1:1 mixture, the *p*H value in the beginning, *i.e.*, when no alkali has been added, is 3.0, which is lower than that of aluminium chloride (3.78) and mandelic acid (5.1) solution alone. This is due to the complex formation as a result of which hydrogen of hydroxyl group of the acid becomes more labile and therefore lowers the *p*H value. This is further confirmed as there is an inflection at two equivalents of alkali, which indicates the formation of 1:1 chelate:



.. (1)

Further addition of alkali brings about a sudden increase in hydroxyl-ion concentration.

Curve C represents *p*H values of 1 : 2 mixture. As in the previous case, the *p*H to start with is less than 3.78. The curve has an inflection at about four equivalents of alkali which indicates that a 1:2 chelate is also formed. The reaction is represented as:

$$2C_6H_5CH\begin{matrix}OH\\COOH\end{matrix} + Al^{3+} = \left[\left(C_6H_5CH\begin{matrix}-O-\\COO\end{matrix}\right)_2 Al\right]^- + 4H^+ \quad .. \quad (2)$$

Here again due to liberation of four equivalents of H^+ions per g. ion of Al, the inflection occurs at four equivalents of alkali.

Curve D represents the *p*H values of 1 : 3 mixtures. There is only one well-defined inflection at six equivalents of alkali, which confirms the formation of 1 : 3 chelate according to the equation :

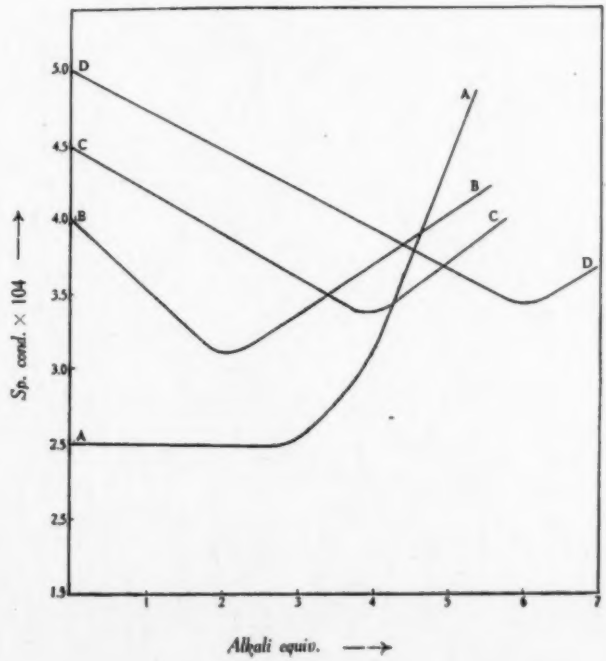
$$3C_6H_5CH\begin{matrix}OH\\COOH\end{matrix} + Al^{3+} = \left[\left(C_6H_5CH\begin{matrix}-O-\\COO\end{matrix}\right)_3 Al\right]^{3-} + 6H^+ \quad .. \quad (3)$$

Similar curves were obtained for concentrations $M/500$ and $M/1000$ also.

Conductance Measurements

Fig. 2 represents the changes taking place in the specific conductance when different mixtures are titrated against a standard alkali. Here the abscissa represents the number of alkali equivalents

FIG. 2



added per g. ion of aluminium and ordinate represents sp. conductance. Curve A, which is for aluminium chloride solution alone, has two inflections at 3 and 4 equivalents of alkali, showing the precipitation of $Al(OH)_3$ and formation of sodium aluminate. Curve B for 1 : 1 mixture has minimum specific conductivity at 2 equivalents of alkali which can be explained as follows.

Due to formation of 1:1 chelate, 2 equivalents of H^+ions/g. ion of Al are set free. Therefore its specific conductance is greater than that of $AlCl_3$ solution in the beginning. On addition of sodium hydroxide, sp. conductance decreases as H^+ions are removed. When all the H^+ions are used up, the specific conductance increases because of excess of OH^-ions. Thus, the curve is actually analogous to the titration curve of strong acid and strong base. Therefore from the position of inflection at two equivalents of alkali, the formation of a 1 : 1 chelate is inferred.

Curve C representing the sp. conductance of 1 : 2 mixture, when titrated against alkali, has got one minimum at four equivalents of alkali. This minimum is attributed to 1 : 2 chelate and corresponds to equation (2). The increase in sp. conductance afterwards is due to excess of NaOH. Similarly in agreement with the theoretical expectation, curve D, which is for 1 : 3 mixtures, shows only one well-defined inflection at six equivalents of alkali required for 1 :3 chelate. As the ratio of the chelating agent is increased, the curves, exhibiting higher complexes, do not denote lower ones as in the presence of excess of chelating ligand, these titrations can hardly show any indication of lower complexes.

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HYDROXY- AND ALKOXY-ALKYLBIGUANIDE METAL COMPLEXES. PART IV. INSTABILITY CONSTANTS OF COPPER AND NICKEL COMPLEXES

By Nihar Ranjan Sengupta and Priyadaranjan Ray

The instability constants of copper and nickel complexes of hydroxy- and alkoxy-alkylbiguanides have been determined spectrophotometrically from a study of their formation reaction in solution. The acid dissociation constants k_{a_2} and k_{a_1} of the ligands have been determined, following the method suggested by Bjerrum (cf. Das Sarma, this *Journal*, 1952, **29**, 217). It has been found that the basic character of the ligand increases with the introduction of a hydroxyl group in the alkyl radical of the substituted biguanide molecules. The stability constants of nickel complexes of hydroxy- and alkoxy-alkylbiguanides are also somewhat greater than those of their corresponding alkylbiguanides.

The present work was undertaken with a view to making a systematic and quantitative study of the influence of hydroxyl and alkoxyl groups in a substituted biguanide molecule on the stability of their complexes with bivalent metals like copper and nickel, as also on the relative stability of the two metallic complexes.

The acid dissociation constants of ethanol-, propanol-, methoxyethyl- and methoxypropyl-biguanides have been determined for this purpose, following the method suggested by Bjerrum ("Metal Ammine Formation in Aqueous Solution", P. Haase and Son, Copenhagen, 1941; cf. Das Sarma, this *Journal*, 1952, **29**, 217).

In acid solutions biguanide is present as biguanidinium ion. In low acid concentration it occurs mostly as s-$BigH_2^+$ ion, the concentration of s-$BigH_3^{2+}$ ion being negligible :

$$\text{s-BigH}_2^+ \rightleftharpoons \text{BigH} + \text{H}^+$$

$$\text{s-BigH}_3^{2+} \qquad \text{s-BigH}_2^+ + \text{H}^+$$

where s-BigH = one molecule of hydroxy- or alkoxy-alkylbiguanide.

Therefore :

$$k_{a_1} = \frac{[\text{s-BigH}]\,[\text{H}^+]}{[\text{s-BigH}_2^+]}$$

and similarly

$$k_{a_2} = \frac{[\text{s-BigH}_2^+]\,[\text{H}^+]}{[\text{s-BigH}_3^{2+}]}$$

The square bracket indicates concentration. The experimental conditions were chosen to ensure a low concentration of the reactants in the presence of a large quantity of 0.2*M*-KCl for maintaining a constant ionic strength.

The values of k_{a_1} and k_{a_2} are obtained from the formation curves traced by plotting $\bar{\eta}$ against the *p*H values (Fig. 1), when $\bar{\eta} = 0.5$ and 1.5 respectively (*loc. cit.*).

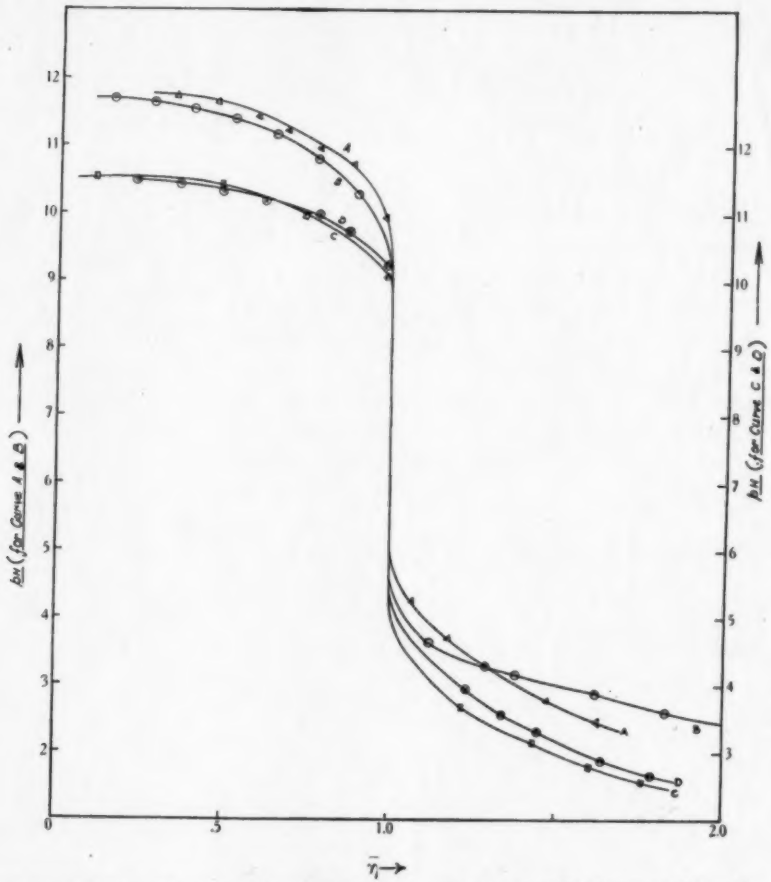
The value of the first acid dissociation constant k_{a_1} of these ligands can be arranged in the following order along with that of ethylbiguanide (cf. Das Sarma, *loc. cit.*) and propylbiguanide (Sengupta and Dutta, unpublished work), for comparison:

$$\underset{4.5 \times 10^{-12}}{\text{Propylbiguanide}} > \underset{3.98 \times 10^{-12}}{\text{Methoxypropylbiguanide}} > \underset{3.38 \times 10^{-12}}{\text{Methoxyethylbiguanide}} \gtrsim \underset{3.39 \times 10^{-12}}{\text{Ethylbiguanide}} >$$

$$\underset{3.16 \times 10^{-12}}{\text{Propanolbiguanide}} > \underset{2.98 \times 10^{-12}}{\text{Ethanolbiguanide}}$$

It shows that the basicity increases with the introduction of a hydroxyl group in the substituent. The alkoxy group in the substituent, on the other hand, exerts little effect on the basicity of the ligand as is evident from k_{a_1} value of the methoxyethylbiguanide, which is practically the same as that of the ethylbiguanide.

FIG. 1



Curve "A"-Ethanolbiguanide. Curve "B"-Propanolbiguanide. Curve "C"-Methoxyethylbiguanide. Curve "D"-Methoxypropylbiguanide.

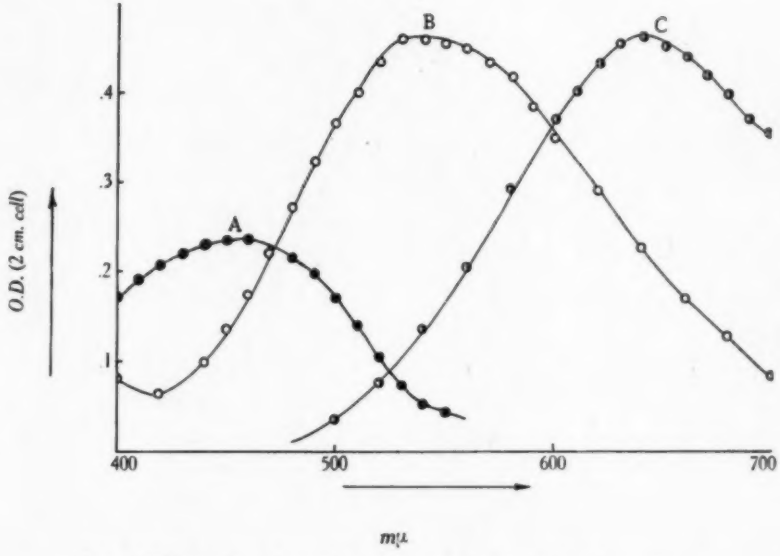
Instability Constants.—The hydroxy- and alkoxy-alkylbiguanides give rise to water-soluble coloured complexes with copper and nickel ions (vide Part I, this *Journal*, 1959, **36**, 373). The instability constants of the complexes have been determined from the measurement of optical density of their solutions.

(*i*). *System : Copper complexes.*—When a metal ion is mixed with hydroxy- or alkoxy-alkylbiguanide solution in the form of chloride (perchlorate or nitrate cannot be used as they form sparingly soluble precipitates) in the molar ratio of 1:3 in the presence of a neutral salt (to maintain

a constant ionic strength), the formation of a coloured complex occurs in solution at certain *p*H values. Up to *p*H 3, the bluish green colour of copper ion persists; this gradually changes to a blue colour (*mono*-complex) above *p*H 3, exhibiting absorption maxima at 650 to 670 mμ, the colour intensity reaching a maximum at *p*H 4 to 5. Above *p*H 5, the solution develops a pink colour (*bis*-complex), having an absorption maximum at 520 to 540 mμ (Fig. 2; also cf. Ray and Rây, *ibid.*, 1959, **36**, 849).

FIG. 2

Absorption spectra of metal complexes.



Curve "A"-Ni-complex. Curve "B"-Cu-*bis*-complex. Curve "C"-Cu-*mono*-complex.

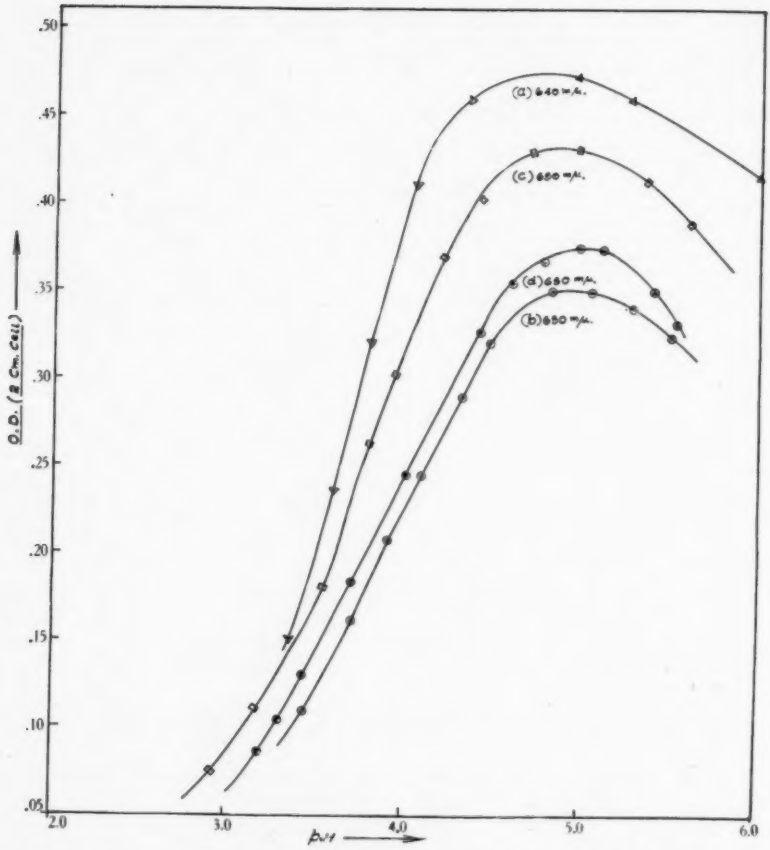
(*ii*). *System : Nickel complexes.*—Nickel develops an orange-yellow colour above *p*H 6.5, with the solution of an excess of a hydroxy- or alkoxy-alkylbiguanide. The colour shows an absorption maximum at 460-480 mμ, characteristic of diamagnetic nickel biguanide complexes (Fig. 3.).

Molar Extinction Coefficient.—The molar extinction coefficients of the blue (*mono*) and pink (*bis*) copper complexes as well as of the nickel complex were evaluated from the optical density values (from the O.D/*p*H curve) measured at the wave-length of absroption maximum of the respective complexes (Figs. 3, 4 and 5). The molar extinction coefficients of copper *mono*-complexes at the wave-length corresponding to the absorption maximum of copper-*bis*-complexes were obtained from

the O.D. values at that wave-length of solutions at *p*H 4 to 5 in which the concentration of the *mono*-complex would become maximum.

FIG. 3

Formation of Cu-mono-*complexes*

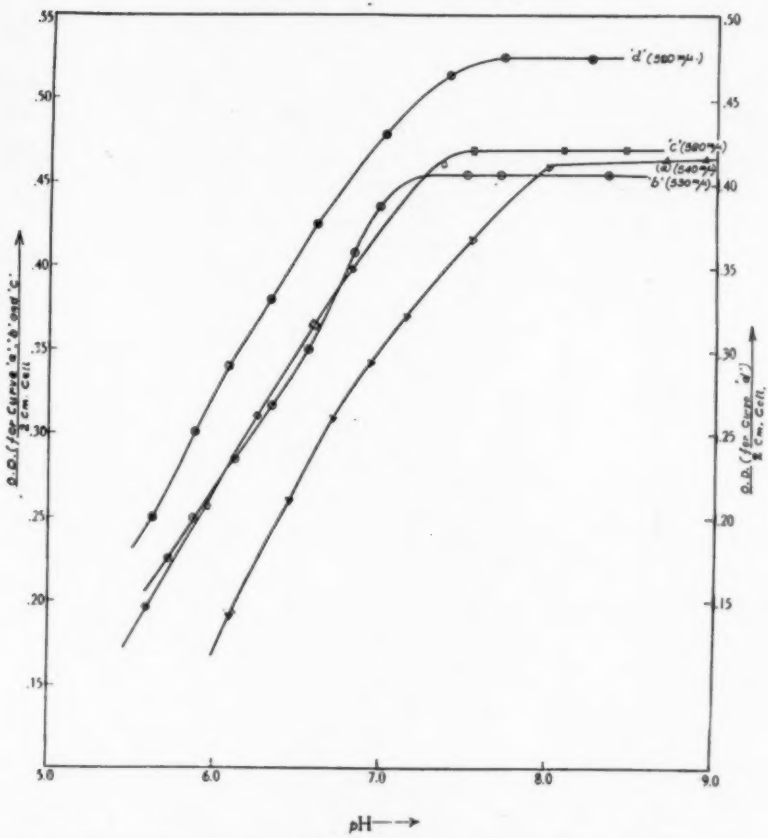


Curve "a"-Ethanolbiguanide. Curve "b"-Propanolbiguanide. Curve "c"-Methoxyethylbiguanide. Curve "d"-Methoxypropylbiguanide.

For the copper-ligand systems depending on the *p*H of the solutions, there may exist two distinct equilibria : (*i*) between the hydrated copper ion (bluish green) and the copper *mono*-complex (blue) and (*ii*) between the copper *mono*-complex (blue) and the copper *bis*-complex (pink). In the case of nickel, however, only one equilibrium, *i.e.*, between the hydrated nickel ion (green) and the nickel *bis*-complex (orange-yellow) has been found to occur.

FIG. 4

Formation of Cu-bis--*biguanide complexes.*



Curve "a"-Ethanolbiguanide. Curve "b"-Propanolbiguanide. Curve "c"-Methoxyethylbiguanide. Curve "d"-Methoxypropylbiguanide.

The interference due to the chloro-complex of copper has been discussed critically by Ray and Rây (*loc. cit.*; 1959, **36**, 858) and in the light of their discussion, the influence of any chloro-complex of copper may be ignored in the evaluation of the stability constants of copper *mono*-biguanide complexes.

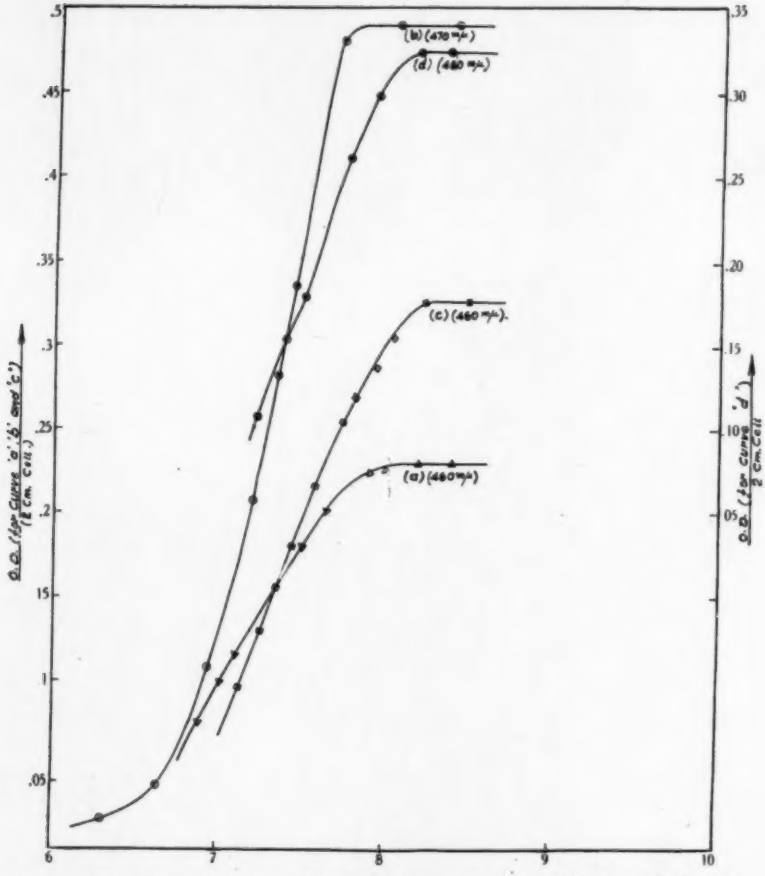
The concentration of any coloured species (A or B) in a system in equilibrium can be calculated from the following equation (cf. Ray and Rây, *loc. cit.*):

$$C_A = \frac{D - \epsilon_B \cdot C}{\epsilon_A - \epsilon_B};\ C = C_A + C_B$$

where ϵ and C signify respectively the molar extinction coefficient and concentration of the coloured species.

FIG. 5

Formation of Ni-bis-*biguanide complexes.*



Curve "a"-Ethanolbiguanide. Curve "b"-Propanolbiguanide. Curve "c"-Methoxyethylbiguanide. Curve "d"-Methoxypropylbiguanide.

Instability Constants

(*a*). *Copper complexes.*—The biguanide salts and the copper ion in solution form complexes like $[Cu\ (s\text{-}BigH)]^{2+}$ and $[Cu\ (s\text{-}BigH)_2]^{2+}$ depending on the *p*H of the solution.

$$Cu^{2+} + s\text{-}BigH_2^+ \rightleftharpoons [Cu(s\text{-}BigH)]^{2+} + H^+ \quad .. \quad (5)$$

$$[Cu\ (s\text{-}BigH)_2]^{2+} + s\text{-}BigH_2^+ \rightleftharpoons [Cu\ (s\text{-}BigH)_2]^{2+} + H^+ \quad .. \quad (6)$$

Hence the equilibrium constants kf'_1 and kf'_2 of the reactions (5) and (6) are given by:

$$kf'_1 = \frac{[Cu\ (s\text{-}BigH)^{2+}] \,.\, [H^+]}{[Cu^{2+}] \,.\, [s\text{-}BigH_2^+]} \quad .. \quad (7)$$

and

$$kf'_2 = \frac{[\text{Cu (s-BigH)}_2^{2+}] \,.\, [\text{H}^+]}{[\text{Cu (s-BigH)}^{2+}] \,.\, [\text{s-BigH}_2^+]} \qquad .. \quad (8)$$

Let $C_2 = [\text{Cu (s-BigH)}_2^{2+}]$, $C_1 = [\text{Cu (s-BigH)}^{2+}]$, α = initial metal-ion concentration and β = initial biguanide concentration.

Therefore kf'_1 and kf'_2 are given by (cf. Ray and Rây, *loc. cit.*):

$$kf'_1 = \frac{C_1 \,.\, [\text{H}^+]}{(\alpha - C_1) \,.\, [\text{s-BigH}_2^+]} \qquad .. \quad (9)$$

i.e.,

$$kf'_1 = \frac{C_1 \,.\, [\text{H}^+] \left\{ 1 + \dfrac{[\text{H}^+]}{k_{a_2}} \right\}}{(\alpha - C_1) \quad (\beta - C_1)} \qquad (10)$$

and

$$kf'_2 = \frac{C_2 \,.\, [\text{H}^+]}{(\alpha - C_2) \,.\, [\text{s-BigH}_2^+]} \qquad .. \quad (11)$$

i.e.,

$$kf'_2 = \frac{C_2 \,.\, [\text{H}^+]}{(\alpha - C_2) \,(\beta - \alpha - C_2)} \qquad .. \quad (12)$$

Now the successive instability constants k_2 and k_1 are derived from:

$$[\text{Cu (s-BigH)}_2]^{2+} \rightleftharpoons [\text{Cu (s-BigH)}]^{2+} + \text{s-BigH}$$

and

$$[\text{Cu (s-BigH)}]^{2+} \qquad \text{Cu}^{2+} + \text{s-BigH}$$

i.e.,

$$k_2 = \frac{[\text{Cu (s-BigH)}^{2+}] \,.\, [\text{s-BigH}]}{[\text{Cu (s-BigH)}_2^{2+}]} = \frac{1}{kf'_2} \times k_{a_1}$$

and

$$k_1 = \frac{[\text{Cu}^{2+}] \,.\, [\text{s-BigH}]}{[\text{Cu (s-BigH)}^{2+}]} = \frac{1}{kf'_1} \times k_{a_1}.$$

Therefore the overall instability constant (K) for copper complex = $k_1 \times k_2$

i.e.,

$$K = \frac{(k_{a_1})^2}{kf_1' \times kf'_2} \qquad (13)$$

(*b*). *Nickel complexes.*—Nickel reacts with hydroxy- or alkoxy-alkylbiguanide in one step to form *bis*-hydroxy- or alkoxy-alkylbiguanide complex:

$$\text{Ni}^{2+} + 2\,(\text{s-BigH}_2^+) \rightleftharpoons [\text{Ni}\,(\text{s-BigH}\,)_2\,]^{2+} + 2\text{H}^+.$$

The equilibrium constant for the reaction is given by:

$$kf' = \frac{[\,\text{Ni}\,(\text{s-BigH}\,)_2^{2+}] \,.\, [\,\text{H}^+\,]^2}{[\,\text{Ni}^{2+}\,] \,.\, [\,\text{s-BigH}_2^+\,]^2} \qquad .. \quad (14)$$

i.e.

$$kf' = \frac{C_0 \,.\, [\text{H}^+]^2}{(\alpha - C_0) \,.\, [\text{s-BigH}_2^+]^2} \qquad \text{(vide copper)}$$

$$= \frac{C_0 \cdot [H^+]^2}{(\alpha - C_0) \cdot (\beta - 2C_0)} \quad .. \quad (15)$$

where $C_0 = [Ni\ (s\text{-}BigH)_2^{2+}]$. Therefore the instability constant K of the nickel complex is derived from :

$$[Ni\ (s\text{-}BigH)_2]^{2+} \rightleftharpoons Ni^{2+} + 2\ (s\text{-}BigH) \quad .. \quad (16)$$

$$K = \frac{[Ni^{2+}] \cdot [s\text{-}BigH]^2}{[Ni\ (s\text{-}BigH)_2^{2+}]} = \frac{1}{kf'} \times (k_{a_1})^2 \quad .. \quad (17)$$

The values of the instability constants of copper and nickel complexes are recorded in Tables I-V.

A comparative statement of the instability of the metal complexes of hydroxyalkyl, alkoxyalkyl and some of the alkyl biguanides are recorded in Table VI. It may be concluded that the introduction of a hydroxyl and a methoxyl group in a substituent in the biguanide moleclue increases the stability of the nickel complexes. The value of the instability constant of the copper ethanolbiguanide complex is somewhat approximate due to a slight hydrolytic reaction leading to the formation of a binuclear copper complex. The nickel complexes are less stable (about 10^{-4} times) than the corresponding copper complexes. Comparing the relative basic strengths of the hydroxy- and alkoxy-alkylbiguanides with the relative stabilities of their copper or nickel complexes, it may be concluded that there is no simple relation between the two. It should, however, be noted that while the formation of the copper complexes occurs through two successive steps, the nickel complexes are formed in a single step.

EXPERIMENTAL

A. Acid Dissociation Constants of Hydroxy- and Alkoxy-alkylbiguanides

A solution of hydroxyalkylbiguanide monohydrochloride (0.05*M*) or of alkoxyalkylbiguanide dihydrochloride (0.05*M*) was prepared from a solution of pure recrystallised hydroxyalkylbiguanide sulphate or alkoxyalkylbiguanide acid sulphate (cf. Part I, *loc. cit.*) by treatment with a little excess of the requisite quantity of barium chloride solution, filtering from the precipitated barium sulphate, and diluting to a definite volume with water. An aliquot of the biguanide hydrochloride solution (0.05*M*, 10 c.c.) was taken in each of several 50 c.c. standard volumetric flasks along with 10 c.c. of KCl (1*M*) solution and to these different amounts of standard hydrochloric acid or caustic potash solutions were added as required and the resulting solutions were made up to 50 c.c. These were kept at $30° \pm 2°$ for a day, and next day the *p*H of the solutions was measured using a glass electrode (up to *p*H 8) or an alkiglass electrode (from *p*H 9 and above), against a saturated calomel reference electrode, in the Cambridge *p*H meter. The *p*H meter was set against a buffer solution of known *p*H. The values of k_{a_1} and k_{a_2} were obtained from the $\bar{\nu}_i$ values plotted against *p*H (Fig. 1).

	Ethanol biguanide	Propanol biguanide	Methoxyethyl biguanide	Methoxypropyl biguanide
$k_{a_1}(\bar{\nu}=0.5)$	2.98×10^{-12}	3.16×10^{-12}	3.38×10^{-12}	3.98×10^{-12}
$k_{a_2}(\bar{\nu}=1.5)$	1.58×10^{-3}	1.00×10^{-3}	1.00×10^{-3}	0.83×10^{-3}

B. Instability Constants of Metal Complexes

A solution of the metal ion (*i.e.* metal chloride) of known strength and that of the biguanide hydrochloride were mixed in the molar ratio (1:3 in the case of copper complexes and 1:3 to 1:6 in the case of nickel complexes) in a 50 c.c. volumetric flask. A large excess of the ligand in the case of nickel complexes was found to be necessary in order to prevent hydrolysis of the complex. The *p*H of the solutions was adjusted to different values by the addition of alkali. A definite amount (10 c.c. of 1*M* solution) of KCl solution was added to each flask before making up the volume. The *p*H and the absorption spectra of solutions were measured (in Unicam SP 600) after allowing the mixture to attain equilibrium at 30° ± 2° for about 24 hours. The results are recorded in the tables.

TABLE I (cf. Fig. 3, curve b)

Formation of copper mono-*propanolbiguanide complex.*

$\alpha = 0.005047M.$ $\quad \epsilon_{\text{Cu-mono-complex}} = 34.67$ $\quad k_{a_1} = 3.16 \times 10^{-12}.$

$\beta = 0.015M.$ $\quad \epsilon_{Cu^{2+}} = 5.00$ $\quad k_{a_2} = 1.00 \times 10^{-3}.$

KCl = 0.2*M*. $\quad$ Wave-length = 650 mμ. $\quad$ Temp. = 30° ± 2°.

*p*H.	O.D (1 cm).	C_1.	$(\alpha - C_1)$.	$(\beta - C_1)$.	$\left[s - BigH_2^+\right] = \frac{(\beta - C_1)}{\left(1 + \frac{[H^+]}{k_{a_1}}\right)}$.	$kf'_1 \times 10^2$.
3.5	0.061	0.001206	0.003841	0.013794	0.01048	0.95
3.6	0.070	0.001509	0.003538	0.013491	0.01078	0.99
3.7	0.080	0.001846	0.003201	0.013154	0.01096	1.05
3.8	0.090	0.002183	0.002864	0.012817	0.01106	1.09
3.9	0.102	0.002587	0.002460	0.012413	0.01103	1.20
4.0	0.112	0.002925	0.002122	0.012075	0.01102	1.25
4.1	0.122	0.003261	0.001786	0.011739	0.01088	1.33
4.2	0.133	0.003634	0.001413	0.011366	0.01070	1.52

kf_1' (average) = 0.0117

$$k_1 = \frac{1}{kf_1'} \times k_{a_1} = 2.7 \times 10^{-10}$$

TABLE II (cf. Fig. 4, curve b)

Formation of copper bis-*propanolbiguanide complex.*

$\alpha = 0.005047M.$ $\quad \epsilon_{\text{Cu-bis-complex}} = 45.10.$ $\quad k_{a_1} = 3.16 \times 10^{-12}.$

$\beta = 0.015M.$ $\quad \epsilon_{\text{Cu-mono-complex}} = 9.32.$ $\quad k_{a_2} = 1.00 \times 10^{-3}.$

KCl = 0.2*M*. $\quad$ Wave-length = 530 mμ. $\quad$ Temp. = 30° ± 2°.

*p*H.	O.D(1 cm).	C_2.	$(\alpha - C_2)$.	$(\beta - \alpha - C_2)$.	$kf'_2 \times 10^5$.
5.8	0.120	0.001699	0.003348	0.008254	9.81
5.9	0.125	0.001839	0.003208	0.008114	8.90
6.0	0.133	0.002062	0.002985	0.007891	8.75
6.1	0.142	0.002314	0.002733	0.007639	8.81
6.2	0.147	0.002453	0.002596	0.007498	7.95
6.3	0.155	0.002677	0.002370	0.007276	7.78
6.4	0.163	0.002900	0.002147	0.007053	7.63
6.5	0.172	0.003152	0.001895	0.006801	7.73
6.6	0.180	0.003375	0.001672	0.006578	7.72
6.7	0.190	0.003655	0.001392	0.006298	8.32

kf'_2 (average) = 8.24×10^{-5}

$$k_2 = \frac{1}{kf'_2} \times k_{a_1} = 0.38 \times 10^{-7}$$

Therefore $K = k_1 \times k_2 = 1.03 \times 10^{-17}$.

TABLE III (cf. Figs. 3 and 4)

Copper complexes.

$\beta = 0.015M$. KCl $= 0.2M$ Temp. $= 30° \pm 2°$. $\epsilon_{Cu^{2+}} = 5.00$.

Complex	ϵ_1 (640 — 650mμ).	ϵ_2 (520 — 540 mμ).	ϵ_1 (520 — 540 mμ).	$kf_1' \times 10^2$.	$k_1 \times 10^{10}$.	$kf_2' \times 10^5$.	$k_2 \times 10^7$.	$K \times 10^{17}$.
Cu-ethanolbiguanide complex (cf. curve a) $a = 0.005M$	47.39	46.88	13.60	2.71	1.10	2.64	1.13	1.24
Cu-propanolbiguanide complex (cf. curve b) $a = 0.005M$	34.67	45.10	9.32	1.17	2.07	8.24	0.38	1.03
Cu-methoxyethylbiguanide complex (cf. curve c) $a = 0.005M$	43.35	47.39	9.48	1.99	1.70	10.39	0.32	0.56
Cu-methoxypropylbiguanide complex (cf.curve d) $a = 0.005M$	37.80	47.88	10.78	1.32	3.02	10.25	0.39	1.17

ϵ_1 and ϵ_2 stand for the molar extinction coefficients of copper-*mono*-hydroxy and alkoxy-alkyl and copper-*bis*-hydroxy- and alkoxy-alkylbiguanide complexes respectively.

TABLE IV (cf. Fig. 5, curve a)

Formation of nickel bis-ethanolbiguanide complex.

$\alpha = 0.002274M.$ $\epsilon_{\text{Ni-complex}} = 51.00.$ $k_{a_1} = 2.98 \times 10^{-12}.$

$\beta = 0.02M.$ $\epsilon_{Ni^{2+}} = 1.00.$ $k_{a_2} = 1.58 \times 10^{-3}.$

KCl = 0.2*M*. Wave-length = 460 mμ. Temp. = 30° ± 2°.

pH.	O.D (1 cm).	C_0.	$(\alpha - C_0)$.	$(\beta - 2C_0)$.	$kf' \times 10^{11}$.
7.00	0.0490	0.0009326	0.0013414	0.0181348	2.11
7.10	0.0575	0.0011040	0.0011700	0.0177920	2.37
7.20	0.0660	0.0012750	0.0009990	0.0174500	2.64
7.30	0.0750	0.0014540	0.0008200	0.0170920	3.04
7.40	0.0850	0.0016550	0.0006190	0.0166900	3.82
7.50	0.0900	0.0017540	0.0005200	0.0164920	3.92

kf' (average) $= 2.98 \times 10^{-11}$

$$K = \frac{1}{kf'} \times k_{a_1}^2 = 2.97 \times 10^{-13}$$

TABLE V (cf. Fig. 5)

Nickel complexes.

$\beta = 0.015\ M.$ KCl = 0.2 *M*. Temp. = 30° ± 2°. $\epsilon_{Ni^{2+}} = 1.00.$

Complex.	$\epsilon_{\text{Ni-complex}}$ (460-470 mμ).	$kf' \times 10^{11}$.	$K \times 10^{13}$.
Ni-propanolbiguanide complex (curve b) $\alpha = 0.005M$	48.71	2.10	4.76
Ni-methoxyethylbiguanide complex (curve c) $\alpha = 0.0025M$	66.69	1.05	10.94
Ni-methoxypropylbiguanide complex (curve d) $\alpha = 0.0024M$	64.21	0.89	17.72

TABLE VI

Ligand.		k_1(Cu) $\times 10^{10}$.	k_2(Cu) $\times 10^{7}$.	Instability constant (overall). $K_{Cu} \times 10^{17}$.	$K_{Ni} \times 10^{13}$.
Ethanolbiguanide	..	1.10	1.13	1.24	2.97
Propynolbiguanide	..	2.70	0.38	1.03	4.76
Methoxyethylobiguanide	..	1.70	0.32	0.56	10.94
Methoxypropylbiguanide	..	3.02	0.39	1.17	17.72
*Biguanide	..	0.80	0.06	0.05	0.33
*Methylbiguanide	..	3.00	0.24	0.72	16.60
*Ethylbiguanide	..	3.70	0.28	1.04	16.63

*Studied by Das Sarma and Ray (this *Journal*, 1956, **33**, 841)

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SYNTHESIS OF NEW LOCAL ANAESTHETICS. PART III

By P. N. Bhargava and K. A. Jose

Piperidinoacetyl-2-amino-, -4-methyl-, -5-methyl-, -6-methyl, -4-chloro-, -6-chloro-, -4-ethoxy-benzothiazoles and their hydrochlorides have been synthesised and their local anæsthetic activity has been tested. The pharmacological screening has shown that the hydrochloride of piperidinoacetyl-2-amino-6-methylbenzothiazole is the most potent of all the compounds described here.

In continuation of the previous work on local anæsthetics (Bhargava and Nair, this *Journal*, 1957, **34,** 42) and 2-aminobenzothiazoles (Bhargava and Baliga, *ibid.*, 1958, **35,** 807), it was considered worthwhile to prepare 2-aminobenzothiazole, 2-amino-4-methyl-, -5-methyl-, -6-methyl-, -4-chloro-, -6-chloro- and -4-ethoxy-benzothiazoles according to the method of Hugershoff (*Ber.*, 1903, **36,** 3121) and to convert these respectively into piperidinoacetyl-2-amino-, -4-methyl--5-methyl-, -6-methyl-, -4-chloro-, -6-chloro- and -4-ethoxy-benzothiazoles, firstly by condensation with chloroacetyl chloride and secondly with piperidine according to Bhargava and Nair (*loc. cit.*). The hydrochlorides of these bases have been prepared and their local anæsthetic activity has been tested.

A study of the pharmacological screening, in accordance with the procedure adopted by Bulbring and Wajda (*J. Pharmacol.*, 1945, **85,** 78), has shown that the hydrochloride of piperidinoacetyl-2-amino-6-methylbenzothiazole is the most successful local anæsthetic out of the six compunds tested and is the most potent compound amongst the methyl derivatives prepared. The hydrochlorides of piperidinoacetyl-2-aminobenzothiazole, piperidinoacetyl-2-amino-4-chlorobenzothiazole and piperidinoacetyl-2-amino-6-chlorobenzothiazole produced good plexus anæsthesia in frogs. Piperidinoacetyl-2-amino-4-methylbenzothiazol and piperidinoacetyl-2-amino-4-ethoxybenzothiazole hydrochlorides also showed good anæsthetic action. It is interesting to note that all these compounds took less time for the onset of anæsthesia than procaine hydrochloride, the standard substance used.

Experimental

2-Aminobenzothiazoles were prepared according to the method of Hugershoff (*loc. cit.*). Their properties and analytical data are recorded in Table I.

Table I

[B denotes bezothiazole. A denotes 2-amino.]

Compounds.	% Yield.	M.P.	Formula.	% Sulphur. Found.	Calc.
1. A-B[a] ..	75	129°	$C_7H_6N_2S$	20.78	21.33
2. A-4-methyl-B[b] ..	68	136°	$C_8H_8N_2S$	19.12	19.51
3. A-5-methyl-B[c] ..	69	143°	$C_8H_8N_2S$	19.01	19.51
4. A-6-methyl-B ..	73	138°	$C_8H_8N_2S$	19.20	19.51
5. A-4-chloro-B[c] ..	75	202°	$C_7H_5N_2ClS$	16.84	17.34
6. A-6-chloro-B ..	67	198°	$C_7H_5N_2ClS$	16.92	17.34
7. A-4-ethoxy-B ..	51	197°	$C_9H_{10}ON_2S$	16.10	16.49

a Hugershoff, *loc. cit.*
b Hunter *et al.*, *J Chem. Soc.*, 1926, 1385.
c Bhargava and Baliga, *loc. cit.*

Chloroacetyl-2-aminobenzothiazole.—Chloroacetyl chloride (2.5 c.c.), dissolved in pure benzene (10 c.c.), was gradually added to 2-aminobenzothiazole (5 g.), dissolved in benzene (30 c.c). The reaction mixture was warmed at 70° on a water-bath for 1½ hours. Benzene was distilled off and the residue was washed with sodium bicarbonate solution and water, and then dried. The product was crystallised from absolute ethanol, m.p. 156°, yield 4.5 g.

Similarly chloroacetyl derivatives of other 2-aminobenzothiazoles were prepared. Their properties and analytical data are mentioned in Table II.

TABLE II

Compounds.	% Yield.	M.P.	Formula.	% Sulphur. Found.	% Sulphur. Calc.
1. Chloroacetyl-A-B ..	58	156°	$C_9H_7ON_2ClS$	14.02	14.13
2. Chloroacetyl-A-4-methyl-B ..	70	180°	$C_{10}H_9ON_2ClS$	13.00	13.30
3. Chloroacetyl-A-5methyl-B ..	80	185°	$C_{10}H_9ON_2ClS$	12.99	13.30
4. Chloroacetyl-A-6-methyl-B ..	70	183°	$C_{10}H_9ON_2ClS$	13.12	13.30
5. Chloroacetyl-A-4-chloro-B ..	62	187°	$C_9H_6ON_2Cl_2S$	12.01	12.26
6. Chloroacetyl-A-6-chloro-B ..	69	202°	$C_9H_6ON_2Cl_2S$	11.98	12.26
7. Chloroacetyl-A-4-ethoxy-B ..	75	185°	$C_{11}H_{11}O_2N_2ClS$	11.90	11.83

Piperidinoacetyl-2-aminobenzothiazole.—To chloroacetyl-2-aminobenzothiazole (4 g.), dissolved in absolute ethanol (40 c.c.), piperidine (4 c.c.) was added and the mixture refluxed for 4 to 5 hours. Alcohol and excess of piperidine were recovered by distillation and the residue was washed with sodium bicarbonate to remove the acid impurities and finally with water. The product was crystallised from 80% alcohol and recrystallised from benzene in yellow crystals, m.p. 85°, yield 3g.

Similarly piperidinoacetyl derivatives of other 2-aminobenzothiazoles were prepared. Their hydrochlorides were also prepared as usual and crystallised from alcohol-ether mixture (1:1). The properties and analytical data of these derivatives are recorded in Table III.

TABLE III

	Piperidinoacetyl-2-aminobenzothiazoles.					Hydrochlorides.		
				% Sulphur.		M.P.	% Chlorine.	
* Compounds.	% Yield.	M.P.	Formula.	Found.	Calc.		Found.	Calc.
1.	50	85°	$C_{14}H_{17}ON_3S$	11.58	11.63	248°	11.10	11.40
2.	58	145°	$C_{15}H_{19}ON_3S$	11.00	11.07	235°	10.60	10.90
3.	45	120°	$C_{15}H_{19}ON_3S$	10.98	11.07	..	..	..
4.	50	90°	$C_{15}H_{19}ON_3S$	11.12	11.07	253°	10.41	10.90
5.	72	130°	$C_{14}H_{16}ON_3ClS$	10.20	10.34	227°	9.98	10.26
6.	54	172°	$C_{14}H_{16}ON_3ClS$	10.28	10.34	256°	9.82	10.26
7.	75	135°	$C_{16}H_{21}O_2N_3S$	9.98	10.03	239°	9.86	9.98

* Piperidinoacetyl derivatives compounds as recorded in Table I.

Pharmacological Test : Plexus Anæsthesia in Frogs.—Hydrochloride solutions, 0.1% and 0.2%, were used and the time of onset of anæsthesia was recorded and compared with that of procaine hydrochloride as a standard substance. The results are shown in Table IV.

TABLE IV

Hydrochloride of piperidinoacetyl—.	With 0.1% solution for onset of anæsthesia in		With 0.2% solution for onset of anæsthesia in	
	0.1*N*-HCl.	0.2*N*-HCl.	0.1*N*-HCl.	0.2*N*-HCl.
1. *Procaine hydrochloride	35.0 mins.	43.0 mins.	32.0 mins.	41.5 mins.
2. -A-B	24.0	29.0	20.5	26.0
3. -A-4-methyl-B	13.5	17.5	11.5	14.5
4. -A-6-methyl-B	9.5	12.0	6.5	8.0
5. -A-4-chloro-B	23.5	33.5	23.5	31.5
6. -A-6-chloro-B	18.5	26.5	18.0	24.0
7. -A-4-ethoxy-B	11.5	16.0	11.5	14.5

It was used as such and not in the form of piperidino derivative.

The study of the pharmacological screening has shown that the hydrochloride of piperidinoacetyl-2-amino-6-methylbenzothiazole is the most active of all the compounds described here and also among the three methyl-substituted derivatives. Piperidinoacetyl-2-amino-4-ethoxybenzothiazole and piperidinoacetyl-2-amino-4-methylbenzothiazole hydrochlorides follow it next in order of pharmacological activity. It is all the more interesting to find that the hydrochlorides of piperidinoacetyl-2-aminobenzothiazoles described require less time for the onset of anæsthesia than the standard substance, procaine hydrochloride, used.

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SHORT NOTES

CHEMICAL EXAMINATION OF THE ESSENTIAL OIL FROM SEEDS OF *DESCURAINIA SOPHIA* (LINN), WEBLE EX-PRANTL, SYN. *SISYMBRIUM SOPHIA* (LINN)

By K. K. Baslas

The plant of *Descurainia sophia* (Linn) belongs to the Family Cruciferae and is distributed widely in temperate Himalayas from Kashmir to Kumaon. The seeds of the plant are bitter, expectorant, restorative, tonic and useful in fevers, bronchitis and dysentery. According to the indigenous system of medicine these seeds are efficacious for worms and calculous complaints. The seeds are also used as a substitute or adulterant of the seeds of *Sisymbrium irio* (Linn) (Kirtikar and Basu, "Indian Medicinal Plants", Vol. I, p. 150).

The fatty oil from the seeds has already been examined and the presence of linolenic, linoleic, oleic, erucic, palmitic and stearic acids reported (Baslas, *Indian J. Appl. Chem.*, 1959, **22,** 122). On steam-distillation of the seeds a foul smelling essential oil was obtained in 0.025% yield.

The oil (200 c.c.) was fractionated in Tower's microfractionating column when the following fractions were obtained :

(I) 119-22° (1.5 c.c.), (II) 151-52° (3 c.c.), (III) 198-200° (2.5 c.c.), (IV) 242-44° (12 c.c.); (V), residue (1 c.c.).

Fraction (IV) forms the chief component, and possesses the following properties which resemble closely with those of benzyl *iso*thiocyanate, as shown in Table I.

Fractions (I) and (II) were identified as allyl cyanide and allyl *iso*thiocyanate respectively. Presence of allyl disulphide was suspected in fraction (III), but no confirmation was obtained for the same. Similarly the presence of propenyl *iso*thiocyanate has been indicated in the residue, but it could not be confirmed.

Isolation of the Oil.—The essential oil was obtained by steam-distillation of the dry seeds from a copper still provided with a copper condenser and extracting the steam distillate with petroleum ether. After removal of the solvent a greenish yellow oil was obtained possessing the following properties : $d^{15°}$ 1.044; $n_D^{15°}$ 1.5278; $[\alpha]_D^{20°} \pm 0$; acid value 23.6 ; ester value 43.

Fractionation.—The oil (20 c.c.) was fractionated in Tower's microfractionating apparatus consisting of a boiling flask (50 c.c.) attached with a standard joint tubulature and a Vigreux column with attached condenser and ground-glass receiver. Careful fractionation yielded five fractions (*vide supra*).

Identification of the Fractions.—Fraction (I) possesses the following properties : $d^{15°}$ 0.8367; $n_D^{15°}$ 1.4048; saponification number 48.2. (Found : C, 71.2; H, 7.5; N, 21.3. Calc. for C_4H_5N : C, 71.64; H, 7.46; N, 20.9%). It was suspected to be allyl cyanide which was confirmed by hydrolysis with alcoholic potash when crotonic acid (m.p. 72°) was obtained.

Fraction (II) was strongly pungent and lachrymatory. (Found : N, 13.9; S, 32.1. Calc. for C_3H_5NCS : N, 14.1; S, 32.3%). It was identified as allyl thiocyanate by preparing a semicarbazide, m.p. 195-96° (Rosenthaler, *Arch. Pharm.*, 1927, **265,** 113) and allylthiourea, m.p. 74-76° (Tornoe, *Ber.*, 1888, **21,** 1288).

Semicarbazide was prepared in the usual way by treating a few drops of the fraction in ethanol with semicarbazide hydrochloride, when a crystalline solid separated after 24 hours.

Allylthiourea was obtained by warming a mixture of 0.5 c.c. of the fraction and excess of ammonia and cooling it subsequently. Confirmation was obtained by mixed m.p. with a genuine sample, when no depression was found.

Fraction (III) strongly smelt like garlic and was suspected to be allyl disulphide. But no solid derivative was obtained excepting a precipitate with silver nitrate solution in alcohol. (Found : S, 43.2. Calc. for $C_6H_{10}S_2$: S, 43.8%).

Fraction (IV) distilled at 138-39°/20 mm and possessed the properties mentioned in Table I. It was identified as benzyl *iso*thiocyanate by preparing its thiourea derivative and phenylbenzyl-thiosemicarbazide. (Found : C, 64.5; H, 4.9; N, 9.9; S, 21.45. Calc. for C_8H_7NS : C, 64.4; H, 4.6; N, 9.6; S, 21.4%).

TABLE I

Properties.	Fraction IV.	Benzyl *iso*thiocyanate.
B.P.	242-44°	243° (*Ber.*, 1868, **1,** 201)
$n_D^{15°}$	1.6044	1.6049 (*J. Chem. Soc.*, 1906, **89,** 564)
Thiourea m.p.	162-64°	164° (Salkovsky, *Ber.*, 1891, **24,** 2724)
Thiosemicarbazide m.p.	156-57°	158° (Blanksma, *Pharm. Weekblad.*, 1914, **51,** 138; *Chem. Zentrl.*, 1915, I, 262).

Fraction (V), the residue, appears to contain propenyl *iso*thiocyanate. (Found : C, 48.5; H, 5.5; N, 13.9; S, 32.1. Calc. for C_4H_5NS : C, 48.48; H, 5.1; N, 14.1; S, 32.3%). No solid derivative could be obtained to confirm the above conclusion based on the consideration of the composition mentioned above. From the amount of various fractions the approximate composition of the oil is as follows : Benzyl *iso*thiocyanate 60%, allyl *iso*thiocyanate 15%, allyl disulphide 12.5, allyl cyanide 7.5% and propenyl *iso*thiocyanate (?), 5%.

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AN IMPROVED PROCEDURE FOR THE PREPARATION OF *sym*-DIARYLTHIO-CARBAMIDES

By Ravindra Pratap Rao

A survey of the literature on the preparation of *sym*-diarylthiocarbamides reveals that the most important method required for this purpose involves the use of the interaction of a primary amine with carbon disulphide according to the following equation :

$$2\,RNH_2 + CS_2 \longrightarrow (RNH)_2CS + H_2S$$

The success of this method depends upon the means employed for effecting the elimination of hydrogen sulphide. The various reagents employed for eliminating hydrogen sulphide are : (*a*) sulphur (Hugershoff, *Ber.*, 1899, **32,** 2245 ; (*b*) potassium or sodium hydroxide (Rathke, *ibid.*, 1873, **5,** 799 ; (*c*) pyridine (Harry *et al.*, *J. Amer. Chem. Soc.*, 1913, **35,** 1539) and (*d*) iodine along with pyridine (Harry *et al.*, *loc. cit.*). Of the four methods, (*b*) and (*c*) are in general use.

In previous investigations on 3-aryl-2-aryliminothiazolid-4-ones and 3-arylthiazolid-2 : 4-diones (this *Journal*, 1955, **32,** 49 ; 1957, **34,** 475 ; 1958, **35,** 576) we had occasion to prepare *sym*-diarylthiocarbamides as starting materials. Studies on the rate of formation of these compounds resulted in a modification of the method (*b*). This deals with the use of concentrated solutions of potassium carbonate or sodium carbonate in the place of KOH or NaOH solutions. This has been found to furnish better yields than (*b*) and (*c*) both. The results of this investigaion are briefly discussed here.

Procedure.—The amine (*o*-toluidine, 5 g.), CS_2 (5 c.c.) and ethanol (5 c.c.) were taken in a r.b. flask fitted with a long reflux condenser and the reagent for eliminating H_2S was slowly added. The mixture was heated on a water-bath by varying the time of reflux ranging from 1½ to 3 hours. CS_2 and ethanol were then distilled off and the residue was washed with water and HCl (dil.) to remove *o*-toluidine, if any. The solid was filtered, washed with water and dried. For each time of reflux the corresponding yield was found out. A small portion of the substance in every case was recrystallised from alcohol and its m.p. determined, which was always found to be 161° (lit. m.p. 161°), thus ensuring the purity of the thiourea, thus obtained. It was further confirmed by determining the percentage of sulphur in some cases.

Table I records the variations in yield on using different reagents for eliminating H_2S. Other details were similar as described in the above procedure.

TABLE I

Reagents used.	Yield in terms of time of reflux.			
	1.5 hrs.	2 hrs.	2.5 hrs.	3 hrs.
40% KOH soln. (4 c.c.) ..	3.51 g.	3.88 g.	4.08 g.	4.67 g.
Pyridine (2 g.) ..	..	2.28	2.66	3.02
40% Na_2CO_3 soln. (5 c.c.) ..	4.51	4.54	4.61	4.82
65% K_2CO_3 soln. (5 c.c.) ..	4.60	4.64	4.76	5.17

The success of this modification can be judged by a careful study of the yields of *sym*-di-*o*-tolylthiourea as given above. Extension of this modification to a variety of amines has also been achieved and it has been found that the modification not only affords better yields but also a high degree of purity of the crude product so that recrystallisation has been found to be unnecessary.

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SYNTHESIS OF SOME CHALKONE-2 : 4-DINITROPHENYLHYDRAZONES

By Durga Nath Dhar*

The usual derivatives used for the characterisation of carbonyl compounds are oxime, semicarbazone and 2 : 4-dinitrophenylhydrazone. The last derivative appears to be of special significance for the characterisation of chalkones on account of the relative ease of its formation. With that end in view the 2 : 4-dinitrophenylhydrazones of several chalkones were prepared. The results are reported in this communication (Table I).

TABLE I

2 : 4-Dinitrophenyl-hydrazone.	Colour & cryst. shape	Crystallised from.	M.P.	Formula.	% Nitrogen. Found.	Calc.
2-Hydroxychalkone-	Brick-red, micro-needles	EtAc	228°	$C_{21}H_{16}O_5N_4$	14.0	13.86
3-Hydroxychalkone-	Bright red, micro-needles	,,	233°	$C_{21}H_{16}O_5N_4$	13.98	13.86
4-Hydroxychalkone-	Bright-red, ** rectangular and hexagonal prisms	,,	231-32.5°	$C_{21}H_{16}O_5N_4$	13.64	13.86
2'-Hydroxychalkone-	Orange, micro-needles	,,	236-37°	$C_{21}H_{16}O_5N_4$	14.0	13.86
2'-Hydroxy-2-methoxy-chalkone-	Orange-red, rod type crystals	,,	225-26°	$C_{22}H_{18}O_6N_4$	13.0	12.90
2'-Hydroxy-3-methoxy-chalkone-	Orange-red, stellate aggregate of micro-needles	Xylene	209°	$C_{22}H_{18}O_6N_4$	12.95	12.90
2'-Hydroxy-3 : 4- dimethoxychalkone-	Brick-red, microcrystalline mass	Ethanol	215-17°	$C_{23}H_{20}O_7N_4$	12.24	12.06
2-Methoxychalkone-	Vermilion, hexagonal plates	EtAc	218-19°	$C_{22}H_{18}O_5N_4$	13.20	13.39
3-Methoxychalkone-	Deep red, microcrystalline powder	EtOH-acetone	214-15°	$C_{22}H_{18}O_5N_4$	13.41	13.39
4-Methoxychalkone-	Orange, slender, micro-needles	EtAc	245-46°	$C_{22}H_{18}O_5N_4$	13.49	13.39
3':4-Dimethoxychalkone-	Red, micro-needles	,,	249-50°	$C_{23}H_{20}O_6N_4$	12.65	12.50

** Pyrochromatic, dark red-hot.

The chalkones required in this investigation were synthesised according to the procedure of Schraufstätter and Deutsch (*Chem. Ber.*, 1948, **81**, 489). The 2 : 4-dinitrophenylhydrazones were prepared by the general method, (Wild, "Characterisation of Organic Compounds", Cambridge University Press, 1947, p. 112) using a solution of the reagent in sulphuric acid and employing a slight excess of the carbonyl compound.

The author wishes to thank the Govt. of India, Ministry of Scientific Research & Cultural Affairs, for the award of a Senior Research Scholarship.

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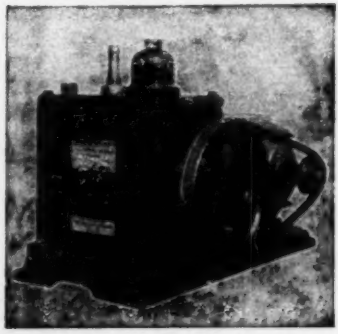

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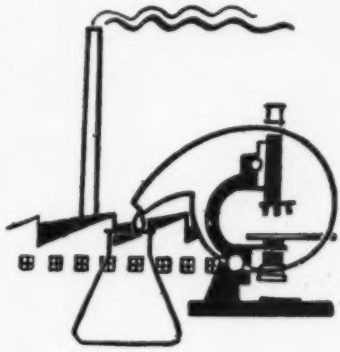

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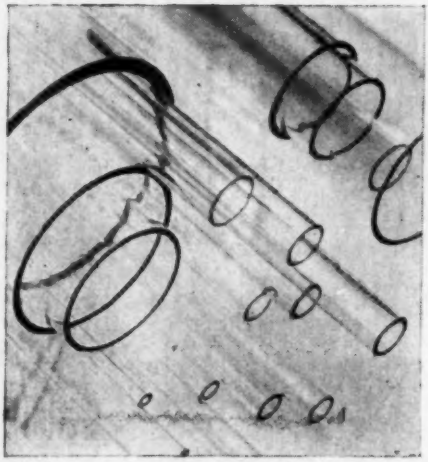

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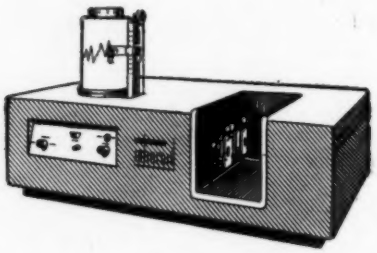

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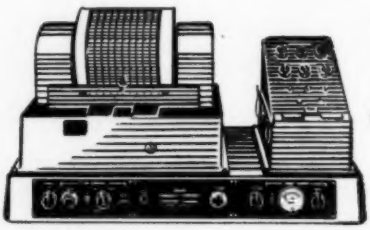

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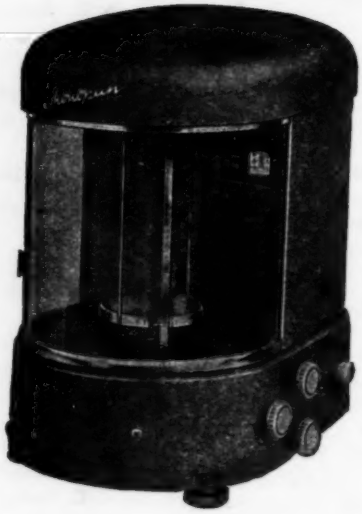

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